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In the second approach, FRC is determined by measuring the compressibility of gas within the chest, which is proportional to the volume of gas being compressed. The patient sits in a body plethys mograph (a chamber usually made of transparent plastic to minimize claustrophobia) and, at the end of a normal tidal breath (i.e., when lung volume is at FRC), is instructed to pant against a closed shutter, thus periodically compressing air within the lung slightly. Pressure fluctuations at the mouth and volume fluctuations within the body box (equal but opposite to those in the chest) are determined, and from these measurements, the thoracic gas volume is calculated by means of Boyle's law (P1V1 = P2V2). Once FRC is obtained, TLC and RV are calculated by adding the value for inspiratory capacity and subtracting the value for expiratory reserve volume, respectively (both values hav ing been obtained during spirometry) (Fig. 296-2). The most impor tant determinants of healthy individuals' lung volumes are height, age, and sex, but there is considerable additional normal variation beyond that accounted for by these parameters. In practice, a mean "normal" value is predicted by multivariate regression equations using height, age, and sex, and the patient's value is divided by the predicted value to determine "percent predicted." For most measures of lung function, 85–115% of the predicted value can be normal; however, in health, the various lung volumes tend to scale together. For example, if one is "normal big" with a TLC 110% of the predicted value, all other lung volumes and spirometry values will also approximate 110% of their respective predicted values. This pattern is particularly helpful in evaluating airflow, as discussed below. AIR FLOW As noted above, spirometry plays a key role in lung vol ume determination. Even more often, spirometry is used to measure airflow, which reflects the dynamic properties of the lung. During an FVC maneuver, the patient inhales to TLC and then exhales rapidly and forcefully to RV; this method ensures that flow limitation has been achieved, so that the precise effort made has little influence on actual flow. The total amount of air exhaled is the FVC, and the amount of air exhaled in the first second is the FEV1; the FEV1 is a flow rate, revealing volume change per time. Like lung volumes, an individual's maximal expiratory flows should be compared with predicted values based on height, age, and sex. While the FEV1/FVC ratio is typically reduced in airflow obstruction, this condition can also reduce FVC by raising RV,

sometimes rendering the FEV1/FVC ratio “artifactually normal” with the erroneous implication that airflow obstruction is absent. The relationships among volume, flow, and time during spirometry are best displayed in two plots—the spirogram (volume vs time) and the flow-volume loop (flow vs volume) (Fig. 296-4). In conditions that cause airflow obstruction, the site of obstruction is sometimes correlated with the shape of the flow-volume loop. In diseases that cause lower airway obstruction, such as asthma and emphysema, flows decrease more rapidly with declining lung volumes, leading to a char acteristic scooping of the flow-volume loop. In contrast, fixed upperairway obstruction typically leads to inspiratory and/or expiratory flow plateaus (Fig. 296-4). RESPIRATORY MUSCLE STRENGTH To measure respiratory muscle strength, the patient is instructed to exhale or inhale with maximal effort against a closed shutter while pressure is monitored at the mouth. Pressures >±60 cmH2O at FRC are considered adequate and make it unlikely that respiratory muscle weakness accounts for any other resting ventilatory dysfunction that is identified. A more sensitive and better tolerated approach to identify inspiratory muscle weakness is performing spirometry in the supine position. This position increases diaphragmatic work by neutralizing the assistance of gravity. FVC in normal subjects decreases approximately 3–8% from upright to supine position, and patients with diaphragmatic weakness, hemidiaphragmatic paralysis, or neuromuscular disease suffer decrements from 10 to >25%. Measurement of Gas Exchange • DIFFUSING CAPACITY (DLCO) This test uses a small (and safe) amount of carbon monoxide (CO) to measure gas exchange across the alveolar membrane during a 10-s breath hold. CO in exhaled breath is analyzed to determine the quantity of CO crossing the alveolar membrane and combining with

hemoglobin in red blood cells. This “single-breath diffusing capacity” (DlCO) value increases with the surface area available for diffusion and the amount of hemoglobin within the capillaries, and it varies inversely with alveolar membrane thickness. Thus, DlCO decreases in diseases that thicken or destroy alveolar membranes (e.g., pulmonary fibrosis, emphysema), curtail the pulmonary vasculature (e.g., pulmonary hypertension), or reduce alveolar capillary hemoglobin (e.g., anemia). Single-breath diffusing capacity may be elevated in asthma, polycythe mia, and pulmonary hemorrhage.

Arterial Blood Gases The effectiveness of gas exchange can be assessed by measuring the partial pressures of oxygen and CO2 in a sample of blood obtained by arterial puncture. The oxygen content of blood (CaO2) depends on arterial saturation (%O2Sat), which is set by Pao2, pH, and Paco2 according to the oxyhemoglobin dissociation curve. CaO2 can also be measured by oximetry (see below): Diagnostic Procedures in Respiratory Disease CHAPTER 297 CaO2 (mL/dL) = 1.39 (mL/dL) × [hemoglobin] (g) × %O2Sat

- 0.003 (mL/dL/mmHg) × Pao2 (mmHg) If hemoglobin saturation alone needs to be determined, this task can be accomplished noninvasively with pulse oximetry. Acknowledgment Edward T. Naureckas and Julian Solway contributed to this chapter in the 21st edition and some material from that chapter has been retained here. ■ ■FURTHER READING Alotaibi NM et al: Mild airways obstruction: Spirometer diagnostic pitfalls. Curr Opin Pulm Med 30:121, 2024. Bates JH: Systems physiology of the airways in health and obstructive pulmonary disease. Wiley Interdiscip Rev Sys Biol Med 8:423, 2016. Haverkamp HC, Balmain BN: Ventilatory response to exercise by age, sex, and health status. Curr Sports Med Rep 23:79, 2024. Hughes JM et al: Effect of lung volume on the

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Mājid Shafiq

Diagnostic Procedures

in Respiratory Disease Diagnostic procedures in respiratory disease encompass a wide array of invasive and noninvasive modalities. Methods for acquiring diagnostic specimens are described in this chapter, as are the various imaging modalities at hand. Pulmonary function tests and measurements of gas exchange are described in Chap. 295.

BEDSIDE PLEURAL PROCEDURES

■ ■THORACENTESIS Thoracentesis, also known as pleurocentesis, refers to percutaneous aspiration of fluid from the pleural space. The right and left pleural spaces do not normally communicate with each other, and either can be directly accessed between the thoracic ribs. The current standard of care entails using point-of-care ultrasonography to mark the site of needle puncture; this reduces the risks of “dry tap” as well as complica tions such as pneumothorax. Beside palliation of symptoms associated with pleural effusion (most commonly dyspnea), thoracentesis may be performed for diagnostic purposes. The range of hematologic, bio chemical, microbiologic, and cytologic pleural fluid studies has largely remained unchanged over the past few decades, as has the widespread adoption of Light’s criteria for distinguishing exudates from tran sudates that were described in 1972. However, newer assays such as mesothelin-1 testing for neoplastic diseases (chiefly mesothelioma) have also become available more recently. More details on pleural fluid testing are described in Chap. 305. PART 7 Disorders of the Respiratory System ■ ■CLOSED PLEURAL BIOPSY Closed pleural biopsy involves percutaneous sampling of the parietal pleural lining. This procedure can be performed either “blindly” (typically with an Abrams needle) or by using imaging guidance such as computed tomography (CT) or ultrasound. Closed pleural biopsy without ultrasound guidance is highly sensitive for pleural tubercu losis, owing to the diffuse pleural involvement that is typically seen in those cases. Image-guided closed pleural biopsy is most helpful in case of focal pleural abnormalities such as pleural nodules, which are virtually pathognomonic of malignant involvement. Limited studies have shown high diagnostic yields of around 80–90% with this modality, but patient selection is key as the diagnostic performance may be considerably lower in the absence of a specific pleural abnormal ity that could be visualized. Between CT and ultrasound imaging, only ultrasound is typically performed in real time during the act of obtaining the biopsy. THORACIC SURGICAL PROCEDURES ■ ■THORACOSCOPY AND

THORACOTOMY Thoracoscopy and thoracotomy encompass a spectrum of surgical procedures that involve accessing and operating within the pleural space, either via one or more small entry ports using thoracoscopic tools or via larger incisions as in thoracotomy (Fig. 297-1). Thoracos copy varies in its scope considerably. An interventional pulmonologist typically performs a pleuroscopy (also known as medical thoracoscopy) and accesses the pleural space through a single port for parietal pleu ral biopsy or for limited therapeutic purposes such as minor lysis of adhesions, thoracoscopic pleurodesis, or indwelling pleural catheter placement. This procedure can usually be performed safely under conscious sedation. On the other hand, video-assisted thoracoscopic FIGURE 297-1 Thoracoscopy demonstrating numerous parietal pleural nodules in a patient with sarcoidosis-related pleural disease. Pleural biopsy revealed nonnecrotizing granulomas. (Source: Ma¯jid Shafiq, MD, MPH.)

surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS) represent more invasive procedures but with more controlled envi ronments entailing general anesthesia with single-lung ventilation, creation of multiple entry ports, and several additional diagnostic and therapeutic possibilities including, but not limited to, lung biopsy, lymph node sampling, lobectomy, decortication, and creation of a pericardial window. Open thoracotomy uses wider incisions and more conventional surgical techniques for performing all of the above as well as additional tasks such as creation of a Clagett window for chronic bronchopleural fistula with empyema. ■ ■MEDIASTINOSCOPY AND MEDIASTINOTOMY Surgical access to the mediastinum, either through a small port (medi astinoscopy) or a wider incision (mediastinotomy), enables diagnostic sampling of mediastinal structures such as mediastinal lymph nodes as part of lung cancer staging. With the advent of endoscopic needlebased techniques (see below), surgery is no longer considered the firstline option for diagnostic lymph node sampling but is recommended in cases of negative needle-based sampling where suspicion for malignant nodal involvement remains sufficiently high. BRONCHOSCOPY Bronchoscopy, which entails passing a tube with a lighted camera inside the lower respiratory tract, includes flexible and rigid bron choscopy (termed after the physical properties of each bronchoscope). Flexible bronchoscopy is by far the more commonly used form and enables access to more distal parts of the respiratory tract. The rigid bronchoscope, although limited to the central airways, has the added advantage of providing a secure airway for ventilation; artificial breaths can then be administered through the scope itself as part of a closed circuit or through open jet ventilation. The rigid bronchoscope also provides a conduit for diagnostic or therapeutic instruments to be passed freely, rather than through the relatively constrained working channel of a flexible bronchoscope. When bronchoscopy is limited to diagnostic indications, the rigid bronchoscope is seldom used except on occasion as a precautionary measure for anticipated severe bleeding where having a more secure airway might be particularly advantageous (e.g., in transbronchial cryobiopsy). Different types of diagnostic bron choscopic procedures are described below. Bronchoalveolar Lavage Bronchoalveolar lavage (BAL) is the gold standard method for obtaining respiratory secretions for hemato logic, biochemical, microbiological, and/or cytologic analyses. It avoids the risk of salivary contamination, which may be seen in a sputum specimen and is particularly useful when sputum cannot be obtained or when sampling of a specific pulmonary lobe or segment is desired. After wedging the bronchoscope in a distal airway in order to prevent fluid escape around the scope, sterile saline or distilled water is instilled through the scope’s working channel (typically in one to three aliquots of ~50 mL each). Immediately thereafter, suction is applied to aspirate as much of the fluid as possible. This allows sampling of distal airways and lung parenchyma—areas not directly viewable

or accessible. If there is concern for alveolar hemorrhage, serial BALs from the same site may show rising red blood cell counts and even visibly bloodier returns with subsequent lavages. Brushing and Endobronchial Biopsy Bronchoscopic brushing is a minimally invasive sampling technique that can be used to sample the mucosal biofilm for microbiologic analyses as well as the bronchial epithelial layer for cytologic analyses. Endobronchial biopsy allows sampling of abnormal bronchial mucosa and submucosa for histopath ologic analysis (as may be indicated in cases of endobronchial amyloi dosis or sarcoidosis, for example). Among cigarette smokers with one or more lung nodules and a nondiagnostic bronchoscopy, bronchial brushings can be used with a commercially available classifier that estimates lung cancer probability based on a gene expression signature. Patients with intermediate pretest probability who end up with low posttest probability can more confidently opt for imaging surveillance, thus avoiding further invasive testing and related complications.

Transbronchial Biopsy Including Cryobiopsy Transbronchial biopsy involves removing a piece of alveolated lung tissue by passing a sampling tool into the alveolar space. The most commonly employed biopsy tool is flexible forceps, typically 2.0 mm or 2.8 mm in caliber. When a specific pulmonary lesion such as a lung nodule is being biop sied, various imaging and navigation tools (described below) may be used to help guide the site of forceps biopsy. When random sampling of the lung parenchyma is desired, e.g., to assess for posttransplant lung rejection, either fluoroscopic guidance or tactile feedback is commonly used to position the forceps in the subpleural lung parenchyma. Lim ited data point to three biopsy samples being adequate for optimizing sensitivity in case of malignant lung nodules. On the other hand, at least five distinct pieces of alveolated lung tissue are needed for formal diagnosis of acute cellular rejection among lung transplant recipients per current recommendations. An increasingly popular biopsy tool is the cryoprobe, a flexible catheter with a blunt tip that delivers liquid nitrogen or carbon dioxide over a few seconds to freeze a portion of lung parenchyma and make it adhere to the probe itself. Before the tis sue can thaw and detach, the probe is pulled back (typically along with the bronchoscope itself), and a frozen piece of lung tissue is removed alongside. Cryobiopsy has a higher diagnostic yield than forceps biopsy for diffuse parenchymal illnesses such as idiopathic pulmonary fibrosis but comes with a higher risk of major bleeding and pneumothorax. Transbronchial Needle Aspiration Transbronchial needle aspi ration (TBNA) involves using a hollow-bore needle for obtaining aspirated specimens. This may be accompanied by suction or simply rely on capillary action, with data not pointing to suction impacting diagnostic sensitivity. TBNA has diagnostic sensitivity superior to that of transbronchial biopsy for malignant peripheral nodules. This makes intuitive sense given that the lesion may lie extraluminally and require traversing the airway wall, which only the needle may be able to accomplish. Furthermore, combining TBNA with conventional transbronchial biopsy appears to increase pooled diagnostic sensitivity. A B FIGURE 297-2 A. Endobronchial ultrasound-guided transbronchial needle aspiration of a mediastinal lymph node. B. Rapid on-site evaluation (ROSE) using Diff-Quik stain indicative of noncaseating granuloma. (Source: Ma¯jid Shafiq, MD, MPH.)

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration Endobronchial ultrasound (EBUS) and EBUS-guided transbronchial needle aspiration (EBUS-TBNA) represent a major advance in diagnostic bronchoscopy over the turn of the twentieth century, largely replacing surgical methods for lymph node sampling. EBUS-TBNA involves using a specialized flexible bronchoscope that simultaneously operates a video camera and a convex ultrasound probe (which is installed at its distal end). Under real-time ultrasonographic visualization, the aspiration needle is inserted

through the airway wall into the mediastinal target and the aspirate is sent for microbiologic or cytologic analyses as indicated (Fig. 297-2). Newer variants of this technique involve the use of core needles or mini-forceps, providing tissue specimens rather than aspirates that can be sent for histopatho logic analysis. EBUS-TBNA has a sensitivity of ~90% for epithelial malignancies and ~70% for lymphoma (higher for detecting cases of lymphoma recurrence than for de novo lymphoma). For sarcoidosis, estimates point to a sensitivity of at least 80% (higher if combined with endobronchial and transbronchial biopsies). EBUS-TBNA has been shown to provide adequate amounts of material to provide ancillary testing in cases of malignancy, such as immunostaining or genetic testing. A related needle-based technique, also using ultrasound guid ance, involves sampling mediastinal structures through the esophagus, which can be a useful adjunct to EBUS-TBNA as it may provide bet ter access to certain mediastinal lymph node stations. The combined sensitivity of these two techniques is slightly higher compared to either one alone. Esophageal sampling can be accomplished either with the standard endoscope used by gastroenterologists for endoscopic ultra sound (EUS) or by inserting the same EBUS bronchoscope through the esophagus (EUS-B).

Diagnostic Procedures in Respiratory Disease CHAPTER 297 At many centers, EBUS-TBNA is accompanied by rapid on-site cytologic evaluation (ROSE), wherein a portion of the aspirated speci men is immediately examined by a cytotechnologist or pathologist using rapid staining. This rapid assessment, while often inadequate for

a definitive final diagnosis, can be helpful in establishing adequacy of sampled material by providing the bronchoscopist with real-time feed back on whether additional sampling is advisable.

The optimal way to process samples obtained via EBUS-TBNA is unknown. Some centers practice the tissue coagulum clot method, in which multiple aspirates are emptied onto a single piece of filter paper to form a clot that can help with preparation of a cell block. Other centers simply use the residue from spun specimens for this purpose. There is no conclusive evidence that one technique is superior to the other, but this question has not been well studied to date. Guided Peripheral Bronchoscopy Including Robotic Bronchoscopy Guided peripheral bronchoscopy involves the use of advanced tools to aid with successful bronchoscopic sampling of peripherally located lesions in the lung parenchyma, such as lung nodules. Prior to 2018, this entailed the use of navigation software and/or real-time imaging while utilizing conventional flexible bron choscopes that were already commercially available. Robotic bron choscopic platforms, first approved for commercial use by the U.S. Food and Drug Administration (FDA) in 2018, were the first to offer additionally improved bronchoscope stability and reach within the peripheral airways compared to conventional flexible bronchoscopes (Fig. 297-3). Early data on the diagnostic performance of robotic bron choscopy, including from small-sized multicenter prospective studies, are encouraging. PART 7 Disorders of the Respiratory System Guided peripheral bronchoscopy comprises three crucial steps:

1. Navigation: Electromagnetic navigational bronchoscopy (which involves GPS-like feedback as the bronchoscope is advanced toward the target) and virtual bronchoscopy (which overlays live endo scopic images onto a CT-derived virtual bronchoscopic map) can help with successful navigation through the airways to the appropri ate lobar/segmental/subsegmental airway. Shape-sensing technol ogy, used as part of one

robotic bronchoscopy platform, also aims to achieve the same purpose. FIGURE 297-3 Use of a robotic navigational bronchoscopic platform for sampling of a 9-mm apicomedial right upper lobe nodule. The navigational software indicates that the lesion is accurately localized (bottom right), as does the concentric image on radial endobronchial ultrasound (bottom left). Biopsy showed non-small cell lung carcinoma. (Source: Ma¯jid Shafiq, MD, MPH.)

2. Localization: The aforementioned technologies can also help local ize a lesion, although they are limited by relying on previously acquired CT images that may or may not accurately represent pre cisely where the lesion is currently located in a three-dimensional space. Radial EBUS uses a thin ultrasound-tipped catheter that can be passed through a bronchoscope's working channel all the way to the lung periphery. This provides real-time images of structures beyond airway walls. A concentric image of the target, indicating a lesion with the airway going through its center, is associated with a high diagnostic yield. Alternatively, radiographic including fluoro scopic imaging can be used to recalibrate the precise target location on navigational bronchoscopic platforms, potentially improving localization as well. Cone-beam CT, which is a distilled version of CT imaging that has been used intraprocedurally in multiple other fields such as interventional radiology, can be used for confirmation of optimal tool-in-lesion (with the patient undergoing a breath hold) prior to sampling.
3. Sampling: The tools available for peripheral sampling include biopsy forceps, brushes, and aspiration needles, as described above, with TBNA having the highest diagnostic sensitivity for malignant lung nodules. Evidence for use of cryobiopsy for sampling discrete lesions in the lung periphery is currently limited but promising. Recent innovations also include real-time ultrasound-guided peripheral sampling (similar to EBUS-TBNA of mediastinal structures) and steerable sampling tools, which hold promise for more optimal sampling of the target lesion. MEDICAL IMAGING Imaging has revolutionized the practice of medicine. Technologies such as x-ray, CT, magnetic resonance imaging (MRI), and positron emission tomography (PET) can provide noninvasive assessments of alveolar perfusion, the metabolic activity of a lung nodule, the bronchovascular source of hemoptysis, or the earliest disease-related changes in parenchymal structure. Given the breadth of advances in respiratory system imaging and increasingly specialized applications across diseases, the following section is organized by technology. The final part of this section is dedicated to deep learning and the role it is increasingly playing in medical image interpretation. ■ ■CHEST X-RAY The field of medical imaging can be traced back to work done by Wilhelm Roentgen in the 1890s. Roentgen noted that after connecting a cathode ray tube to a power supply, material in his lab would fluo resce even if the emission of visible light from the tube was blocked. He quickly deduced the presence of additional invisible "x-rays" and subsequently observed that their passage through solid material was attenuated in proportion to the material's density. Within weeks of its discovery, x-ray technology was being widely leveraged to guide surgi cal exploration and the extraction of foreign objects such as shrapnel from the battlefield. Chest x-ray (CXR) has since become the founda tion of clinical practice for respiratory medicine and is a widely avail able technology even in resource-limited settings. The most commonly used CXR images for respiratory medicine are the posteroanterior (PA) and lateral films in the outpatient setting and anteroposterior (AP) films for those studies obtained at the bed side. These are two-dimensional representations of three-dimensional

structures, and the differing views can be used to examine super imposed structures (e.g., a parenchymal opacity in the retrocardiac space). The contours of the chest wall, the silhouette of the heart, great vessels, and mediastinum, as well as the appearance of the paren chyma and bronchovascular bundle are all used to detect and classify disease as well as monitor its progression or response to therapeutic intervention. An example of a normal PA and lateral CXR is provided in Fig. 297-4. In this image of the normal lung, many of the smaller structures such as the lymphatics and distal airways are beyond the ability of conventional x-ray technology to resolve. Larger structures such as the pulmonary vasculature may also be indistinct because of body position

A B FIGURE 297-4 Posteroanterior (A) and lateral (B) chest x-ray of a normal healthy subject. (Source: George Washko.) and the redistribution of blood flow to more gravitationally dependent regions. Diseases involving these structures may enhance or obscure their appearance. An example of these diseases is congestive heart fail ure where the lymphatics become engorged (Kerley B lines), the non dependent vasculature more prominent (cephalization), and the outer boundaries of the bronchial walls blurred (bronchial cuffing). Each of these findings must be clinically contextualized, and while a thickened interstitium may be due to hydrostatic pulmonary edema, it may also be indicative of interstitial lung disease or carcinomatosis. CXR can also be used to discriminate pulmonary and extrapulmonary disease, and because of that, it is an excellent initial diagnostic for nonspecific symptoms. An elevated hemidiaphragm, fibrosis of the mediastinum, or hyperlucency of the lung parenchyma all reflect processes that cause dyspnea, but their treatment and prognosis differ markedly. ■ ■COMPUTED TOMOGRAPHY CT was introduced to clinical care in the 1980s and quickly became one of the most heavily leveraged modalities for medical imaging. While CXR provides one or two views of the thorax from which an experi enced clinician must disambiguate overlying structures, CT provides spatially resolved reconstructions of all structures in the thorax. The acquisition of a CT scan involves the same basic process as an x-ray with a patient placed between a source of photons and a detector, but the image reconstruction and advanced analytics that can be applied to those images differ markedly. The passage of photons through the body is impeded in proportion to tissue density. This absorption or attenu ation of photon passage is measured in Hounsfield units (HU), and clinical CT scanners are regularly calibrated to a standard scale with water having an HU of 0 and air –1000 HU. The broad range of tissue densities (reflected as attenuation values) in the thorax and the limited human ability to visually discriminate between two structures of simi lar densities are addressed by modifying the image display. A window width and level (the range and center of the range of HU values to dis play) is selected to optimize viewing structures of interest. For example, lung windows are optimized for visual inspection of the low-density lung parenchyma and all of the surrounding higher-density structures appear white, whereas the mediastinal windows are optimized to view the higher-density structures and anything of lower tissue density such as the lung parenchyma appears black. This does not change the HU values of the voxels (three-dimensional pixels) in the image, just their presentation for visual inspection.

 The visual interpretation of thoracic CT is based on the appearance of the secondary pulmonary lobule. This structure is a fundamental subunit of the lung consisting of a central airway and pulmonary artery, parenchyma, and then surrounding interstitium with the lym phatics and pulmonary veins (Fig. 297-5). Processes affecting the small airways such as respiratory bron chiolitis may appear as centrilobular nodules.

Parenchymal diseases such as emphysema may begin by effacing the centroid of the lobule (centrilobular emphysema [CLE]), the periphery of the lobule (para septal emphysema [PSE]), or diffusely across the lobule (panlobular emphysema [PLE]). Pathology of the lymphatics or interstitium (inter stitial lung disease [ILD]) results in beading and/or thickening of the interlobular septa. Examples of many of these processes are provided in Chaps. 303 and 304. The diagnostic information provided by the appearance of the secondary pulmonary lobule is further augmented by the distribution of these patterns of injury across the lung. Whereas CLE tends to first appear in the upper lung zones, PLE has a predilection to be basilar predominant. Interstitial thickening in the apices is more likely to be nonspecific interstitial pneumonitis (NSIP), while a basal and depen dent predominant distribution of that same process is more consistent with idiopathic pulmonary fibrosis (IPF). Finally, morphology of the central airways and vessels can be used to diagnose disease and estimate its severity. Bronchiectatic dilation of the airways may be cylindrical and predominantly in the lower lobes, as is seen in chronic obstructive pulmonary disease (COPD), or be cystic dilation in the upper lobes (cystic fibrosis), or there may be a focal non specific dilation of an airway due to prior infection. Pathologic dilation of the airways may also be due to disease of the surrounding paren chyma. Because of the mechanical interdependence of the bronchial tree and parenchyma, conditions that reduce lung compliance may result in traction bronchiectasis. This may be a local process or more diffuse depending on the distribution of the underlying parenchymal disease and likely provides further insight into disease severity. The caliber of the central pulmonary arterial (PA) trunk proximal to its first bifurcation is directly related to pulmonary arterial pressure. A measure of >3 cm is suggestive of the presence of elevated pulmonary vascular pressures, and more recent studies have demonstrated that an increased ratio of the PA diameter to the diameter of the adjacent aorta (PA/A) provides a metric of disease severity and, in the case of chronic respiratory diseases such as COPD, is prognostic for both

Bronchiole wall thickness 0.05–0.1 mm Acinar artery and bronchioles diamter 0.5 mm Interlobar septa thickness 0.1 mm Visceral pleura thickness 0.1 mm Acinus 0.6–1 cm Respiratory bronchiole PART 7 Disorders of the Respiratory System Terminal bronchiole Lobular bronchiole diameter 1 mm wall thickness 1.05 mm A Pulmonary vein Lobular artery Lobular bronchiole B FIGURE 297-5 A. Illustration of the anatomy of the secondary pulmonary lobule. B. Computed tomography image showing the visible anatomy of the secondary pulmonary lobule. (Panel A adapted from WR Webb: Thin-section CT of the secondary pulmonary lobule: Anatomy and the Image–The 2004 Fleischner Lecture. Radiology 2006;239:322; Panel B source from Samuel Yoffe Ash, MD.) acute respiratory exacerbations and death. Assessment of the intrapa renchymal pulmonary vasculature is typically augmented through the intravenous infusion or bolus of iodinated contrast. This bolus and subsequent image acquisition may be timed to visualize passage of contrast through the pulmonary arteries to enable detection of throm boembolic disease, which appears as dark filling voids in otherwise bright white vessels. It must be noted that the acquisition of CXRs and thoracic CT scans involves exposing the patient to ionizing radiation. Several studies have estimated the excess numbers of cancer due to CT scanning, and exten sive efforts have been made by both CT manufacturers and clinicians to reduce the radiation dose to the lowest possible amount that does not jeopardize image quality and interpretability. ■ ■MAGNETIC RESONANCE IMAGING MRI is based on the behavior of protons in a magnetic field. A strong magnetic field is applied to align the protons, and then a pulse of radio frequency current is applied to the subject. This perturbs the protons, and the speed at which they subsequently realign differs based on the

Pulmonary vein diameter 0.5 mm Lobular artery diameter 1 mm properties of the tissues within the region of interest. While this tech nique provides exquisite imaging data for the chest wall or solid organs such as the brain or heart, the abundance of air in the lung creates an artifact that impairs direct assessment of the parenchyma. For this reason, MRI of the lung leverages intravenous contrast agents such as gadolinium and is increasingly exploring the use of inhaled agents such as hyperpolarized noble gas. These respective agents enable in vivo assessments of organ perfusion and detailed measures of the morphol ogy of the distal airspaces. An example of noble gas–enhanced MRI is shown in Fig. 297-6. The inhaled agent is 3He, and because it is proton rich, it can be used to examine lung ventilation visually and objectively. Regions of the lung that are poorly ventilated due to disease of the air ways or distal airspaces have low concentrations of 3He and appear as dark regions in an otherwise bright blue organ. While an MRI may have a longer acquisition time than CT, and the geometry of the equipment often leads to a sense of claustrophobia, it does not involve the administration of ionizing radiation. This makes it a modality of choice in the pediatric population or clinical situations where repeated assessments are required.

Healthy Asthma FIGURE 297-6 Noble gas magnetic resonance. Healthy control on left and asthma on right. (Images courtesy of Grace Parraga, PhD, Department of Medical Biophysics, Department of Medicine, School of Biomedical Engineering, Robarts Research Institute, Western University, London, Ontario, Canada.) ■ ■POSITRON EMISSION TOMOGRAPHY PET generates an image based on the aggregation of radiolabeled tracers. The most common agent used for these purposes is [18F]- fluoro-2-deoxyglucose (FDG). This radiolabeled glucose analogue is administered intravenously and is taken up by cells in direct pro portion to their metabolic activity. In the clinical setting, it is most commonly used for the discrimination of benign and malignant lung nodules, as well as lung cancer staging. Given the relatively low resolu tion of PET, co-registration with CT is common and the aligned imag ing modalities allow the reader to determine the structural source of heightened metabolic activity. There is increasing interest in the use of PET imaging in the bio medical community. These applications are largely still confined to research, but advances in areas such as in vivo assessments of vascular biology in acute and chronic disease have been impressive. ■ ■ARTIFICIAL INTELLIGENCE/DEEP LEARNING The final aspect to thoracic imaging that must be discussed is the grow ing field of artificial intelligence and deep learning applied to image analysis. Classic machine learning approaches to medical image inter pretation involve the development of advanced algorithms to detect structures of interest, segment their boundaries, and then extract metrics related to size, shape, texture, and so on. The massive increase in processing capacity afforded by graphical processing units (GPUs), the increasing availability of large amounts of data, and the wide dis semination of open-source software libraries allowing developers to create powerful work environments have led to explosive growth in the utilization of deep learning for image analytics. Some of the first medical applications of deep learning were in the field of dermatology, and more recently, this advanced form of pattern recognition has been reported to excel at the discrimination of benign and malignant lung nodules in thoracic CT scan. The breadth of application of these tools continues to expand to include image navigation and feature detection, biomarker development, and direct prediction of clinical outcomes. An example of deep learning–enabled segmentation of the heart and pul monary vasculature from non–contrast-enhanced non–cardiac-gated CT scan is shown in Fig. 297-7. ■ ■TRANSTHORACIC NEEDLE ASPIRATION Radiologically guided needle biopsy has served as a long-standing mechanism for evaluation of parenchymal lung lesions, both malignant and infectious. In the setting of

published guidelines recommend ing low-dose screening CT scan for lung malignancy in high-risk patients, and with evolving guidelines for monitoring and assess ment of incidental lung lesions arising in this setting, radiologically guided sampling of lung lesions has become an increasingly important mechanism to address parenchymal lung abnormalities concerning for cancer. Moreover, as novel immune modulators and biologic agents are increasingly utilized for the management of systemic disease and transplantation, effective interventions are becoming progressively more important in assessing for potential pulmonary infections aris ing as complications of immune suppression. Transthoracic needle

Diagnostic Procedures in Respiratory Disease CHAPTER 297 FIGURE 297-7 Arterial/venous segmentation of the pulmonary vasculature (blue: arteries; red: veins) and epicardial surface of the right (blue) and left ventricles (red). (Image courtesy of Raul San Jose Estepar, PhD, Applied Chest Imaging Laboratory, Department of Radiology, Brigham and Women's Hospital, Boston, MA.) aspiration (TTNA) remains one important arm in the assessment of these pulmonary complications. TTNA can be accomplished with a variety of complementary imag ing mechanisms, including under fluoroscopic, CT, ultrasound, or MRI guidance. Overall adequacy of sampling as well as adequacy for epidermal growth factor receptor (EGFR) analysis of >90% and for cytologic analysis of >80%. CT is currently the most common imag ing modality used to assess parenchymal lung lesions, with sensitivity and specificity reported to be >90%. Sensitivity of CT-guided TTNA is increased in more peripheral lesions. Transthoracic ultrasound has the advantages of a low complication rate in the setting of fine-needle aspiration (FNA) and portability, allowing for more logistical simplic ity in the setting of lung lesion assessment. In a prospective study of ultrasound-guided percutaneous FNA compared with CT-guided FNA, diagnostic rates were comparable between the two groups, with shorter procedure time associated with ultrasound guidance, numeri cal suggestion of decreased complication rate using ultrasound guid ance, and lower costs associated with ultrasound guidance. Use of elastography to better characterize lung lesions has also been proposed in the context of ultrasound, although additional diagnostic yield has not yet been proven. Color Doppler ultrasonographic imaging has been demonstrated to have a high sensitivity and specificity and a low complication rate in another study. Electromagnetic guidance, unlike CT imaging, can be used in combination with endobronchial ultrasound and/or navigational bronchoscopy in the operative setting, theoretically allowing for a multimodal approach that could increase diagnostic yield and allow for a combined staging procedure. Electro magnetic TTNA alone has demonstrated an 83% diagnostic yield in a pilot study, with an increase to 87% when combined with navigational bronchoscopy. Conflicting data are available regarding the diagnostic superiority of TTNA compared with alternative biopsy modalities such as endobronchial ultrasound for diagnosis of lung lesions, and results may depend on center experience. Transthoracic sampling can be obtained using FNA or core needle biopsy. In one retrospective study, FNA was found to have an inferior diagnostic rate, compared with core needle sampling, as well as lower specificity. In this study, a method involving two FNA passes was com pared to core needle sampling with six cores obtained from a single pass. No significant differences in complication rates were noted. In another retrospective study, in which procedure was determined by operator preferences, core needle aspirate samples were more likely to

provide sufficient material for molecular testing than FNA. A system atic review of these techniques concluded that insufficient evidence was available to support a difference between FNA and core needle biopsy in diagnostic efficiency, though core needle biopsy may be more spe cific in

diagnosing benign lung lesions. Given the negative predictive value estimate of 70%, negative results from TTNA are less reliable than positive results and should not be considered definitive to eliminate the concern for malignancy. Further assessment is needed to directly com pare imaging modalities for TTNA guidance and to compare TTNA with other diagnostic modalities to determine the optimal choice of procedure in particular settings. Choice of procedure should be consid ered in the context of the size and location of the lesion, the experience of the center and operator, and patient-specific factors.

PART 7 Disorders of the Respiratory System In regard to the safety of TTNA, in a retrospective study from 2015, the presence of mild to moderate pulmonary hypertension in patients did not increase complication rates in the setting of TTNA. The complication rates noted in this report were substantial, however, with hemorrhage occurring in one-third to one-quarter of patients, and pneumothorax in 17–28%. The majority of pneumothoraces did not require chest tube placement. Other complications included hemoptysis and hemothorax, though these were uncommon. These complication rates are consistent with those reported in other stud ies. In a meta-analysis of complication rates of CT-guided TTNA, complication rates were higher with core needle aspirates than FNA (38.8% [95% confidence interval (CI) 34.3–43.5%] vs 24% [95% CI 18.2–30.8%]). The majority of these complications were minor. Risk factors for complications with FNA included smaller nodule diameter, larger needle diameter, and increased traversed lung parenchyma. No clear risk factors were noted for complications after core needle biop sies in this publication. More generally, the risks of TTNA increase for more centrally located lesions and those residing in close proximity to intrathoracic vasculature. In a study of patient claims in the Medicare and a subset of the commercial population between 2016 and 2020, the use of TTNA decreased in both groups, with the use of endobronchial ultrasound guidance for sampling increasing in the Medicare popula tion. In this study, TTNA presented a higher risk for pneumothorax than the use of alternate modalities. Despite the outstanding questions regarding the context and optimal approach for TTNA, this modality has been shown to be effective in cancer diagnosis in the thorax. Adenocarcinoma has become the most prevalent parenchymal lung malignancy in reported studies and also the most common malignant diagnosis found on TTNA of the lung. TTNA can also be effective in diagnosing less common tumors of the lung, both malignant and benign, including squamous and small cell carcinomas, lymphomas, and others, as well as in assessing tumors of the mediasti num. The diagnostic utility of TTNA is consistent across solid, subsolid, and partially calcified lung nodules. Immunocytochemistry markers can be utilized in TTNA samples to assist with diagnosis, prognosis, and prediction of response to therapy, and samples should be preserved whenever possible to allow for these studies, if needed. RNA extraction has also proven feasible in the setting of a single FNA sample, which could be instrumental in gene expression profiling, though this has thus far only been successfully accomplished in a research context. The utility of TTNA in diagnosing pulmonary infections is variable in published literature. Some publications have reported that TTNA establishes a diagnosis of infection in 60–70% of cases, with a particu larly high yield in the setting of Aspergillus infections. TTNA has also been shown to be particularly effective in the diagnosis of pulmonary tuberculosis, though a wide variety of infections have been diagnosed using this method. The presence of necrosis in lung lesions makes establishing an infectious diagnosis more likely using TTNA. Numer ous staining techniques are available to assist with infectious diagnoses, and immunohistochemistry can also aid in the diagnosis of infection. Cytology should be correlated with histopathology and culture results, when available. Metagenomics using next-generation sequencing for detection of infection is evolving but requires

further study. TTNA has also been useful in identifying granulomatous inflammation, which can provide supportive evidence of a granulomatous parenchymal lung disease in the appropriate clinical setting.

In summary, TTNA is an important element of diagnostic algo rithms in the setting of lung nodules and masses, particularly when concern for malignancy is not high enough to warrant immediate excision, when the patient is not a surgical candidate, or the lesion or disease is not amenable to surgical resection. Further study is needed, however, to better understand the role of TTNA and other diagnostic modalities in the evaluation of parenchymal lung lesions. MISCELLANEOUS TESTING ■ ■SPUTUM TESTING Sputum microscopy and culture are commonly utilized to diagnose respiratory tract infections and identify the causative organisms. In patients with productive cough, the sampling is simple and noninva sive; however, it is subject to patient technique and the potential for oropharyngeal and/or upper respiratory tract contamination. In those who are not expectorating, sputum induction can be considered using provocative nebulization with saline. This technique has been demon strated to be generally safe and well tolerated even in patients with air flow limitation. Numerous studies have attempted to define criteria for reliability and reproducibility of sputum samples. The majority include quantification of number of epithelial cells and white blood cells per low-power field, and many assess the ratio of the two for adequacy of sampling. None has been confirmed as superior in establishing the reli ability of sampling to reflect lower respiratory tract growth. The quality of the sputum sample directly impacts the diagnostic reliability in the setting of bacterial pneumonia. Growth of Mycobacterium tuberculosis, Legionella, or pneumocystis should raise concern for infection, even in the setting of a poor sample. In a prospective study of the use of a multiplex polymerase chain reaction (PCR) assay in conjunction with sputum sampling, good-quality samples had a higher proportion of bacterial detections than low-quality samples but equivalent frequency of samples with bacterial growth in patients who received treatment. In this study, 40% of bacterial detections would have been missed if only high-quality samples were analyzed. The authors conclude that all sam ples submitted for PCR-based testing should be analyzed, regardless of sputum sample quality. In systematic analyses and meta-analyses, mul tiplex PCR assays have been shown to decrease the time to diagnosis and length of stay in the setting of viral infections and in patients with COVID-19 and bacterial co-infection. Endotracheal aspirates have not been demonstrated to be clearly superior to expectorated sputum in terms of diagnostic reliability, but such sampling may be required if spontaneous coughing is nonproductive and induced sputum is not feasible or successful. The use of multiplex fluorescence PCR may allow for assessment of multiple pathogens with a reduced time to pathogen identification. As in the context of infection, sputum cytologic analysis has been utilized to assist in the diagnosis of malignancy, mainly because it can be obtained noninvasively. While sputum cytology demonstrating malignant cells is highly specific for a diagnosis of lung malignancy, its sensitivity has been reported at <40%. A systematic review of screening methods demonstrated no added benefit from sputum cytology when combined with CXR to screen for lung cancer. Advanced molecular techniques such as PCR, DNA methylation markers, micro-RNA assessment, and tumor-related protein analysis have been proposed in sputum assessment for diagnostic purposes and risk stratification. At present, however, sputum cytology is recommended only when more invasive techniques cannot be pursued, such as in patients with pro hibitive comorbidities or in resource-limited settings. ■ ■EXHALED BREATH CONDENSATE Exhaled breath condensate includes gaseous, liquid, and water-soluble components, with numerous biomarker types and collection system varieties developed over time. Validation standards for many compo nents are still being determined. Exhaled nitric oxide is the most highly validated of the biomarkers identified in

exhaled breath condensate. The fraction of exhaled nitric oxide (FeNO) has been demonstrated in higher concentrations in exhaled breath condensate of patients with asthma than in healthy individuals, has been shown in a systematic

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