3.1 X-Ray

3.1.1 Quotation

Chest X-ray radiography is a common auxiliary means in the diagnosis and treatment of critical care. It can provide information about the course of the disease and cardiopulmonary status. And in the critical care unit, patients often need a variety of life-supporting catheters, X-rays can help clinicians determine the location of these catheters and whether there are other complications during the placement of the catheters. Routine chest X-rays can help doctors determine if treatments are effective and manage potential complications.

Since the X-ray is such an important thing, how do we confirm its quality? Rubinowitz AN et al. summarized a series of judgment processes [1]. The first step is to assess the quality of the image technically, then clinicians should focus on the location of patients’ catheters such as stomach tube, tracheal cannula, and all other support devices. The next step is to assess the patient’s condition. Clinicians should systematically evaluate patients’ cardiopulmonary status, size of heart border, look for the effusion of the lung and pleural. Then, clinicians should not forget to compare the current X-ray image with the prior studies and evaluate whether the patient is recovering or getting worse.
3.1.2 Applications

3.1.2.1 Monitoring and Support Devices

Endotracheal and Tracheostomy Tubes

Endotracheal intubation is common in patients requiring short periods of mechanical ventilation. Improper placement of the endotracheal tube is very common. The location of endotracheal intubation can be simply determined by auscultation to determine whether the respiratory tone of the left and right lung is symmetrical. However, for patients in the critical care unit, the lung is often damaged, so the stethoscope method may not provide accurate information. So, clinicians always choose bedside X-ray to evaluate the endotracheal tube’s location. With the patient’s head in a neutral position, the proper position of the endotracheal tube is its tip should be located 3–5 cm above the carina [2]. Too deep or too shallow placement of the tube can lead to bad results. Endotracheal tube insertion into the right main bronchus is common because the right main bronchus is thicker and straighter. Deep insertion may lead to hyperventilation of the lung on this side or even lead to pneumothorax, and may lead to contralateral atelectasis. Shallow endotracheal intubation may increase the risk of catheter prolapse or laryngeal injury. Another poorly positioned catheter is that the catheter strays into the esophagus, which, if not detected in time, will lead to excessive accumulation of gas in the gastrointestinal tract, and even lead to gastrointestinal perforation.

The tracheostomy tube is used in patients undergoing prolonged mechanical ventilation. The best position for a tracheostomy tube should be to align its tip with approximately the T3 level. Figure 3.1 shows the right main bronchus intubation.

Enteric Tubes

Gastric tubes are often used for drainage and nutritional feeding. For feeding use, the catheter tip should reach at least to the gastric antrum to reduce the risk of aspiration. Radiology is important for detecting abnormal catheter locations and preventing potentially fatal complications. The catheter may be coiled in the pharynx or esophagus, with a high risk of aspiration. Occasionally, a catheter may cause perforation of the pharynx and pharyngeal capsule. Figure 3.2 shows this situation.

Venous Catheters

Central venous catheters are commonly used for fluid rehydration, parenteral nutrition, or CVP monitoring. To reduce the risk of thrombosis, the central venous catheter tip should be located inside the superior vena cava and outside the venous flap [3]. When the catheter is too deep, it can enter the right atrium, increasing the risk of arrhythmias and heart perforations.
**Fig. 3.1** Right main bronchus intubation. This patient’s chest radiograph demonstrates the endotracheal tube tip in the right main bronchus.

**Fig. 3.2** A gastric tube was accidentally inserted into the right lung. The chest radiograph demonstrates an aberrant enteric tube terminating in the right upper lobe.
Sometimes a catheter goes into an artery, which is often seen in the subclavian artery or common carotid artery. Bright red blood ejections from the catheter are usually observed when the catheter is inserted into the artery, but this may not be evident in ICU patients with heart failure or hypotension, so X-ray examination is still needed to confirm its position. Subclavian venipuncture is of particular concern because it may result in hemothorax, pneumothorax, or chylothorax.

### 3.1.2.2 Pulmonary Parenchymal Abnormalities

#### Atelectasis

Atelectasis, or a decrease in the volume of air in the lungs, is the most common cause of chest X-ray opacity in ICU patients [2]. The most common atelectasis is in the lower-left lobe, followed by the lower right lobe and the upper right lobe [4].

The X-ray manifestations of atelectasis can be classified into direct X-ray signs and indirect X-ray signs. Direct signs include reduced lung transparency in the atelectasis part, an increase in the density of uniformity. In the convalescence period or with bronchiectasis, X-ray may appear uneven density of the cystic transparent area.

Lobular atelectasis is generally in the shape of obtuse and triangular, with broad and pure surfaces facing the costal diaphragmatic pleural surfaces, and the tips pointing to the hilum of the lungs, while the indirect X-ray signs of atelectasis show lateral displacement of the interlobar fissure to atelectasis. As the lung volume shrinks, the bronchi in the lesion area converge with the vascular texture, while the compensatory expansion in the adjacent lung causes the vascular texture to be sparse and shift to the atelectatic pulmonary arch. Clinicians may also see hilum shadow shifting to atelectasis, the hilum shadow shrinks and disappears, and is separated from the dense shadow of atelectasis. Mediastinal, heart, and trachea are shifted to the affected side, especially when the whole lung was atelectasis. However, the more sensitive and accurate diagnosis of atelectasis is CT. Figure 3.3 shows an image of atelectasis.

#### Pneumonia

ICU patients have a higher incidence of pneumonia due to long-term invasive respiratory support and complex conditions. The X-ray manifestation of pneumonia has a certain relationship with the pathogenic bacteria of infection. It may be performed as a multi-focused, focal consolidation on chest radiographs. Pneumonia may be difficult to distinguish from other causes of lung opacity, such as atelectasis, aspiration pneumonia, and pulmonary edema. Figure 3.4 shows an example of bacterial pneumonia.
Fig. 3.3 Atelectasis. The chest radiograph shows the central space-occupying lesion of the right lung and the right upper lobe obstructs atelectasis

Fig. 3.4 Pneumonia. Panels (a) and (b) show X-ray and CT images of pneumonia, respectively. The radiograph demonstrates bilateral lung inflammation with partial consolidation

Pneumothorax

Pneumothorax can result from underlying lung disease, inappropriate respiratory support levels, and medical procedures. Most of the pneumothorax radiographs have clear pneumothorax lines, that is, the boundary line between atrophic lung tissue and the gas in the pleural cavity, showing an outward convex line shadow, the pneumothorax line is a transparent area without lung texture, and the line is
compressed lung tissue. Mediastinal and cardiac migration to the healthy side can be seen in a large amount of pneumothorax. The gas-liquid level can be seen with pleural effusion (Fig. 3.5). For patients in the ICU, chest radiographs in the supine position are often performed. Such patients often do not show the traditional pneumothorax images in chest X-ray, but deep sulcus may be observed [5]. In the supine position, as the pneumothorax increases in volume, the intrapleural air accumulates from the anteromedial region to the laterocaudal region (Fig. 3.6). Hence, the

**Fig. 3.5** Pneumothorax. Upright chest radiograph showing a right apical pneumothorax. A thin line of visceral pleura is visible (arrows). The right lung is about 95% compressed

**Fig. 3.6** Pneumothorax. Panel (a) shows “Deep sulcus sign”, which can be seen in supine patients. It demonstrates lucent deep lateral costophrenic sulcus and lucency of the right lower hemithorax. Panel (b) shows the CT scan taken on the same day which confirmed the presence of pneumothorax in the right thorax
so-called deep sulcus sign is performed as a deep and lucent costophrenic angle which extends more inferiorly than usual. But so far, the golden standard for the diagnosis of occult pneumothorax is still the CT scan.

Pleural Fluid

Pleural effusion is common in ICU patients. The presence of pleural effusion in sitting or standing chest radiographs is indicated by the appearance of a blunt costophrenic angle. However, chest radiographs in the supine position are not sensitive to the diagnosis of pleural effusion and may present only as hazy opacification pulmonary images. CT examination can not only confirm the presence of pleural effusion but also reveal the pulmonary, mediastinal, and pleural conditions, suggesting the etiology of pleural effusion. Figure 3.7 shows the image of layering pleural fluid under X-ray.

3.2 Lung and Diaphragm Ultrasound

3.2.1 Introduction

Ultrasound is a noninvasive technology and has been employed for the bedside assessment of the lung reliably. As a versatile imaging technique, ultrasound provides insights into the presence of lung consolidation, pleural effusion, or interstitial-alveolar syndrome, especially, it allows the possibility of gaining regional
In recent years, ultrasound has played a crucial role in bedside assessment of the critically ill among imaging techniques. In 1942, a neuroscientist Karl Dussik first introduced the use of an ultrasound machine as a medical diagnostic tool [6] and André Dénier first described the diagnostic application of ultrasound [7]. More importantly, in 1989, the Fraçois Jardins intensive care team introduced the application of lung ultrasound in emergency care. Since 1991, point-of-care ultrasound (POCUS) has been used by intensive care physicians for the diagnosis of intensive care medicine. In recent years, the International Consensus Conference on lung ultrasound has standardized nomenclature, technique, and indications to use lung ultrasound in critical care practice [8]. Ultrasound evaluation of diaphragm function and structure is accurate, safe, and noninvasive. Bedside ultrasound was used to evaluate the diaphragm function by measuring the diaphragm activity, diaphragm thickness, and the change rate of diaphragm thickness. It was used to identify the diaphragm dysfunction and the loss of diaphragm function.

### 3.2.2 Lung Ultrasound

#### 3.2.2.1 Selection of Lung Ultrasound Probe

Conventional examination modes are divided into B-mode and M-mode. B-mode ultrasound is a mode in which a linear or convex probe scans an anatomical plane and then converts it into a two-dimensional image. M-mode ultrasound is a mode to record the reciprocating motion of a structure toward or away from the probe. Different probes have their own characteristics. Generally, high-frequency probes have weak penetration capacity, but high resolution. On the contrary, low-frequency probes have strong penetration capacity, but low resolution. Firstly, according to the patient’s body shape and chest wall thickness, low-frequency probes (convex array or phased probe, frequency 1–5 MHz) which can detect a certain depth are usually selected; secondly, high-resolution high-frequency probes (linear array probe, frequency 5–10 MHz) can be selected for pleural lesions or pneumothorax according to the location of the lesions. For obese patients, low-frequency probe is recommended to detect pleural lesions.

#### 3.2.2.2 Operational Skills

Ultrasound examination of the lung does not require a high level of ultrasound section, which can be scanned vertically or parallel to the coastal space. Generally, each side of the chest wall is divided into three parts [9, 10] by the front axillary line and the rear axillary line. Each part is further divided into upper and lower parts, that is, each side of the chest is divided into six areas, a total of 12 bilateral areas, corresponding to different parts of the lungs. Lung ultrasound should be performed by left-right contrast, and all intercostal spaces in each region should be examined in sequence. The probe should be perpendicular to the thorax and slide along the
longitudinal and transverse direction. When the probe is placed in a sagittal position and the angle is adjusted perpendicular to the long axis of the rib space, the marker points generally point to the head side and slip from the head to the foot in the vertical rib space. Most of the pleura can be observed, but the ribs will cover it. Transversely, the probe is placed horizontally along the long axis of the intercostal space, with the marker point facing the sternum and sliding along the long axis of the intercostal space. The whole pleura of the intercostal space can be observed, but it is limited to the pleura of the intercostal space.

3.2.2.3 Image Interpretation

Understanding lung ultrasound images requires familiarity with basic lung ultrasound signs. Because ultrasound cannot penetrate the air, the lungs are the main air-containing organs, combined with the obstructive effect of thoracic bone structure, so the lung has been regarded as the forbidden area of ultrasound examination. However, the lung is an organ of liquid and gas blending. Any lung lesion is accompanied by the change of liquid–gas ratio, and the detection of liquid by ultrasound is sensitive, the change of gas and liquid in the alveoli and interstitium of damaged lungs will produce some ultrasound images and artifacts, which make it possible for lung ultrasound. With the decrease of the ratio of gas to liquid in the lung, the lung lesions, or changes from normal gasified lung tissue to mild interstitial edema, severe interstitial edema and alveolar edema, or from focal to diffuse, eventually develop into consolidation, and even pleural effusion and pneumothorax.

3.2.2.4 Bat Sign

Bat sign is one of the most important signs in lung ultrasound. When the probe is placed vertically in the intercostal space, the bat sign can be seen (Fig. 3.8). The images depict upper and lower adjacent ribs, rib echo ultrasound, and pleural lines, which correspond to the lung surface.

**Fig. 3.8** Lung ultrasound sign. Red arrow shows hyperechoic pleura line with adjacent ribs on both sides (blue arrow)
### 3.2.2.5 Lung Glide Sign

The pleural line moves synchronously with respiratory motion and appears in normal lung tissue. The extent of lung glide reached its maximum in the lower part of the lung, when the lung was descending toward the abdomen. Under B-mode ultrasound, visceral and parietal pleura slipped relatively, and under M-mode ultrasound, hyperechoic pleura line moved to and fro with respiratory motion. Lung glide sign is not obvious in the condition of lung hyperinflation and emphysema. The disappearance of lung glide sign can be seen in pneumonia, atelectasis, pneumothorax, weak breathing, apnea, pleural adhesion, airway obstruction, or one-lung ventilation.

### 3.2.2.6 A-Line

The high echo artifacts parallel to the pleural line under B-mode ultrasound are called line A (Fig. 3.9). Normal subpleural air-filled lung tissue or intrapleural air because of pneumothorax prevents ultrasonic penetration. The strong reflex of chest wall soft tissue and air-filled lung surface forms line A, which is several times deeper than the distance between skin and pleural line. When subpleural gas is evenly distributed, line A can appear, such as normal lung tissue and pneumothorax. When subpleural gas is unevenly distributed, line A will blur or disappear, such as pulmonary interstitial lesions and alveolar lesions.

### 3.2.2.7 B-Line

The hyperechoic vertical line from the pleural line to the distal end is line B (Fig. 3.10). Because of the increase of fluid volume in lung tissue, ultrasound produces strong reverberation at the interface between air and water. Normally, the thickness of subpleural interlobular septum is about 0.10–0.15 mm, mostly less than
the resolution of ultrasound (about 1 mm). Therefore, under normal circumstances, most of them are surrounded by strong echoes of alveolar gases and cannot be displayed. There should be less than two B-lines in each intercostal space.

### 3.2.2.8 Signs of Interstitial Syndrome

Alveolar interstitial syndrome is defined as the presence of three or more adjacent B-lines in a coastal space, which may be limited or diffuse. Linear and convex probes can measure the average distance between B-lines. B-line interval is about 7 mm, suggesting interlobular septal thickening, interstitial pulmonary edema, or lesion; Multiple B-lines with spacing less than 3 mm indicate alveolar pulmonary edema or lesion. The more severe pulmonary edema presents as diffuse B-line. Line B has seven characteristics: comet tail sign; from a pleural line; high echo; laser sample; no attenuation, direct to the edge of the screen; erase line A; and move with the lung sliding.

### 3.2.2.9 Tissue-Like Sign

Pulmonary tissue has no echo or liver tissue-like echo, and there are irregular boundaries with different depths (Fig. 3.11). The occurrence of lung consolidation suggests that the density of lung tissue changes in this area. Similar to line B, there may be an increase in extravascular lung water or a significant decrease in lung ventilation in this area.

### 3.2.2.10 Debris Sign

Short-line, debris-like, strong echo spots appear at the junction of consolidated and air-filled alveoli, which are called debris signs (Fig. 3.11). Ultrasound images of lung consolidation are varied at different stages, if the gas in the consolidated lung
tissue is not fully absorbed, ultrasound shows high echo when it meets gas. In particular, inflammatory lung consolidation occurs in the stage of severe insufficient ventilation and incomplete absorption of air in the lung tissue, ultrasound images can show inhomogeneous bright/dark echoes, similar to debris, so it is called debris sign.

### 3.2.2.11 Bronchial Inflation Sign

Bronchial inflation sign is a heterogeneous, tissue-like (similar to liver echoes) ultrasound image with a punctate or linear hyperechoic sign. It is also an ultrasound sign in the process of pulmonary consolidation. The reason for this is that the air in the bronchus, which is inside consolidated lung tissue, is not fully absorbed; ultrasound produces a bright echo when it meets gas (Fig. 3.11). According to the dynamic changes of bronchial gas with respiratory motion, there are static bronchial inflation signs and dynamic bronchial inflation signs. Dynamic bronchial inflation sign can rule out the diagnosis of obstructive atelectasis. A small sample study found that dynamic bronchial inflation sign was more common in inflammatory lung consolidation and static bronchial sign was more common in atelectasis. For some inflammatory lung consolidation, bronchial fluid filling signs can also be seen.

### 3.2.2.12 Pulmonary Pulsation

Pulmonary pulsation is an early and dynamic diagnostic sign of complete atelectasis. Under normal conditions, the slippage of two pleura layers hinders the vibration of pleural line caused by cardiac activity observed by M-mode ultrasound. When the
main bronchial obstruction or one-lung ventilation leads to complete atelectasis, visceral and parietal pleura slide disappears. Under these conditions, pleural line vibration caused by heart beating can be recorded by M-mode ultrasound. The disappearance of lung glide sign under B-mode ultrasound and the pulsation of pleural line with the beating of heart under M-mode ultrasound is called pulmonary pulsation.

3.2.2.13 Stratospheric Sign (Bar Code Sign)

In M-mode imaging, the normal appearance of the lungs is similar to that of the beach. The extrapleural structure presents as a horizontal line parallel to the probe surface, similar to the sea. The lung parenchyma moves with the respiratory cycle and presents a grainy image, similar to the sand on the coast (Fig. 3.12a). In pneumothorax, the pleura is separated from the parietal layer and the visceral layer due to the air contained in the pleural cavity. In M-mode imaging, the absence of parenchymal movement beneath the pleura will produce multiple horizontal parallel lines, replacing the sandy appearance of the coastal marker. This kind of image is similar to bar code or stratosphere, so it is called stratosphere (bar code) sign (Fig. 3.12b).

3.2.2.14 Pulmonary Point

The pulmonary point is a special ultrasound sign in the diagnosis of pneumothorax. In the same image, one side of the lung tissue has the phenomenon of lung sliding and pulsation, while the other side does not exist. This critical point is called a
pulmonary point. This phenomenon is a specific manifestation of pneumothorax. Under B-mode ultrasound, B-line disappeared, A-line and lung glide disappeared, while under M-mode ultrasound, the critical point of ultrasound sign replacing coastal sign was lung point. The principle is that when pneumothorax occurs, ultrasound detects the boundary of lung tissue compressed by gas. Ultrasound detects the side of pneumothorax, showing that lung glide disappears, and the side of normal lung tissue, showing that lung glide exists. But not all pneumothorax has pulmonary point, when the scope of pneumothorax is large or the examination is incomplete, it may not be able to find the pulmonary point, and pulmonary bullae can also be shown as pulmonary point.

3.2.2.15 Quadrilateral Sign/Sinusoidal Sign

Under B-mode, the quadrilateral anechoic zone in the thoracic cavity was found, with four boundary areas being the upper and lower ribs in the intercostal space where the probe was located, and the visceral and parietal pleura. The anechoic zone was pleural effusion (Fig. 3.13). Under M-mode ultrasound, sinusoidal curves can be seen, indicating the regular displacement between the visceral pleura moving with pulmonary expansion and contraction and the relatively fixed pleura line. This phenomenon often occurs at the costophrenic angles of the base of the lung.

3.2.2.16 Curtain Sign

During examination at the base of lung, images of the diaphragm, liver/spleen, or spine disappear as the lung expands during inspiration and appear as the lung volume decreases during expiration. This phenomenon occurs under normal ventilation; when there is pleural effusion or consolidation of pulmonary tissue, the phenomenon weakens or disappears.

Fig. 3.13 Lung ultrasound sign. The non echo area of the quadrangle shown by the arrow is surrounded by the pleura line of the parietal layer, the upper and lower ribs, and the pleura line of the visceral layer.
3.2.3 Application of Lung Ultrasound

Ultrasound is a fast, noninvasive, and real-time imaging method. Lung ultrasound has been gradually improved and standardized. It plays an important role in the diagnosis, treatment, and judgment of disease changes.

3.2.4 Diagnostic Value of Pulmonary Ultrasound in Respiratory Diseases

Several guidelines suggest that procedure guidance and diagnostic assessment by ultrasound can provide bedside information quickly [8, 11–13]. POCUS for diagnostic assessment is of extensive use in intensive care units [14]. POCUS in the emergency department alongside standard diagnostic tests is superior to standard diagnostic tests alone for establishing a correct diagnosis within 4 h [15].

3.2.4.1 Community-Acquired Pneumonia (CAP) and Ventilator-Associated Pneumonia (VAP)

According to the type of pneumonia, the imaging manifestations are different. Ultrasound signs of pneumonia are heterogeneous B-line; pleural abnormalities, mostly small pulmonary consolidation under pleura; debris sign; or bronchial inflation sign. Inflammatory consolidation manifests differently in different stages. Gas is not fully absorbed in the lung tissues of the lesions, which can be manifested as debris sign, accompanied by bronchial inflation sign, mostly dynamic bronchial inflation sign, or can be manifested as liver-like pulmonary tissue when the gas is fully absorbed. The application of lung ultrasound in screening or diagnosing of CAP or VAP has attracted much attention. 70–97% of CAP patients can see lung consolidation accompanied by bronchial inflation sign [16–18]. Consolidation has 93% sensitivity and 98% specificity in the diagnosis of CAP [17]. However, for ICU patients, pulmonary consolidation and bronchial inflation sign can also occur in patients without pneumonia, which is related to long-term bedridden, controlled ventilation, and systemic inflammatory response. It seems that pulmonary ultrasound has limited value in the diagnosis of VAP. However, some scholars regard linear or tree-like dynamic bronchial images as one of the signs of VAP diagnosis, and can easily calculate the clinical ultrasound score at the bedside for early VAP diagnosis. It may even be better than the traditional clinical pulmonary infection score (CPIS) [19].

3.2.4.2 Pulmonary Edema

B-line is the most important ultrasound sign of pulmonary edema. It may be related to alveolar or interstitial exudation. According to the distribution and shape of B-line, it can be divided into homogeneous B-line, heterogeneous B-line, and
converged B-line. The B-line distribution of pulmonary edema due to elevated hydrostatic pressure was more homogeneous, and there was no change of pleural line, and pleural sliding was not affected [20]. The distribution of B-line in osmotic pulmonary edema shows that the non-dependent area is lighter, the dependent area is heavier, and even the signs of pulmonary consolidation appear. In addition, because of the high viscosity of the exudated fluid, the pleural sliding sign usually weakens or even disappears. Pulmonary edema due to elevated hydrostatic pressure is usually secondary to cardiac insufficiency and volume overload. Cardiac echocardiography can show a significant decrease in systolic function and an increase in the diameter of inferior vena cava. Osmotic pulmonary edema is usually secondary to severe infections and other factors, with normal cardiac function or enhanced systolic function without volume overload.

3.2.4.3 ARDS

The pulmonary lesions of ARDS are heterogeneous. Qualitative imaging evaluation of pulmonary exudative lesions and consolidation by lung ultrasound can assist the diagnosis of ARDS [21–23]. The international consensus on lung ultrasound also suggests the diagnosis of ARDS if there are the following signs: (1) inhomogeneous B-line; (2) abnormal pleural line signs; (3) subpleural consolidation of anterior chest wall; (4) normal pulmonary parenchyma; and (5) weakening or disappearing of pulmonary glide sign [8]. The Berlin definition of ARDS [24] suggests a rapid differential diagnosis of pulmonary edema for suspected ARDS patients without risk factors by echocardiography. Therefore, combined cardiopulmonary ultrasound is helpful for real-time diagnosis of ARDS at bedsides, and can differentiate pulmonary edema, atelectasis, pleural effusion, chronic heart failure, pulmonary interstitial fibrosis, and other pulmonary conditions leading to hypoxemia.

3.2.4.4 Atelectasis

Atelectasis can be divided into compressive atelectasis and absorptive atelectasis. The former is usually caused by a large amount of pleural effusion, with sharp and smooth edges, moderate echo, and jellyfish-like shape with the beating of heart and movement of breath, the compressive atelectasis can be reduced or even disappeared after puncture and drainage. The latter is caused by airway obstruction, such as secretions or tumors. Lung ultrasound shows alveolar consolidation and homogeneous hypoechoic structures resembling liver-like structures. Compared with pneumonia, absorbable atelectasis has no dynamic bronchial inflation sign. Bronchial inflation sign is static (initial stage) or nonexistent (total air is reabsorbed in small airways). If bronchial inflation sign is dynamic, obstructive atelectasis can be excluded [25]. Sometimes bronchial fluids can be found, which suggests that secretions or fluids fill the airway.
3.2.4.5 Pleural Effusion

Ultrasound can directly identify pleural effusion and consolidation [26]. Compared with bedside chest radiographs, ultrasound for detecting pleural effusion showed higher accuracy (93% vs. 47%) [8]. Pleural effusion manifests as an echo-free area in dependent region [27, 28].

The appearance of pleural effusion under ultrasound can indicate the nature of the fluid. Pleural effusion can be characterized by anechoic, complex non-encapsulated, complex encapsulated, or homogeneous echo [29]. Generally, complex pleural effusion suggests exudation, whereas anechoic effusion may be transudate. However, transudate can also be manifested as complex non-encapsulated effusion [29]. This is because the transudate is not only water, but also has different components (such as cells, proteins, and fats). Transudate can also behave as an echo-free liquid. Homogeneous echo effusion is a manifestation of hemorrhage or empyema. In some cases, ultrasound images can help to judge the nature of the effusion. For example, thickened pleural or pulmonary consolidation with bronchial inflation sign (suggesting the site of infection) usually indicates exudate. Diffuse pulmonary congestion (B-line) indicates transudate because of heart failure. In supine position, in transverse scanning, the pleural space at the bottom of the lung is 5 cm or larger, which can predict 500 mL or more pleural effusion. The linear relationship between them was also determined. The pleural space per centimeter corresponded to 200 mL effusion [30, 31]. The application of ultrasound in chest puncture can reduce the number of pneumothorax cases and improve operation efficiency, even for more experienced operators [32].

3.2.4.6 Pneumothorax

The sensitivity, accuracy, and negative predictive value of lung ultrasound in the diagnosis of pneumothorax are much higher than those of chest X-ray and are close to those of CT [24], especially for traumatic patients [33, 34]. When diagnosing pneumothorax by lung ultrasound, we need to recognize the pleural sliding sign, pulmonary pulsation sign, B-line, consolidation, and pulmonary point. Pneumothorax can be diagnosed when the pleural slip sign disappears, the stratospheric sign and the pulmonary point are found by pulmonary ultrasound. If the pulmonary point appears below the midaxillary line, it indicates that at least 30% of the pulmonary parenchyma collapses [35].

Although the specificity with the signs described above for diagnosis of pneumothorax is almost 100%, in most cases, it is difficult to determine the pulmonary point because of the different degrees of pulmonary compression and sometimes focal pneumothorax in severe patients. Therefore, when pneumothorax is suspected in clinical practice, one by one lung tissue should be examined, if pleural sliding sign, pulmonary pulsation sign, B-line, consolidation, and pleural effusion can be found, the presence of pneumothorax in the examination site can be excluded.
3.2.4.7 Pulmonary Embolism

Studies have shown that combined cardiopulmonary and vascular ultrasonography can diagnose pulmonary embolism more accurately [13, 36]. Other studies have shown that the specificity and sensitivity of combined cardiac, pulmonary, and vascular ultrasound in the diagnosis of pulmonary embolism are significantly higher than that of single cardiac, pulmonary, or vascular ultrasound, which can significantly improve the diagnosis of suspected pulmonary embolism and reduce the examination rate of CT pulmonary angiography [37, 38]. Because pulmonary embolism mainly affects the oxygenation of patients by affecting the ratio of ventilation to blood flow, there is usually no obvious lung lesion in patients. Ultrasound signs of pulmonary embolism are mainly line A, sometimes wedge consolidation caused by pulmonary infarction, but rarely accompanied by line B or large areas of pulmonary consolidation. In addition, the presence of deep venous thrombosis in lower extremities can be determined by ultrasound screening of lower extremity vessels thus providing indirect evidence for the diagnosis of pulmonary embolism.

3.2.5 Differential Value of Pulmonary Ultrasound in Etiology of Respiratory Diseases

The bedside lung ultrasound in emergency (BLUE) protocol provides a simple method to analyze and diagnose diseases, using the characteristics of lung ultrasound. This diagnostic scheme can diagnose five common causes of respiratory failure in 90.5% of cases of acute respiratory failure [39]. Traditional medical examination methods include medical history and physical examination. The combination of electrocardiogram and echocardiography with BLUE improves the diagnostic accuracy. The first objective of the BLUE program is to quickly diagnose and treat dyspnea symptoms. The second goal is to reduce the use of computed tomography and X-ray avoiding radiation hazards to special patients such as pregnant women [40, 41]. At the same time, the program allows accurate diagnosis of acute respiratory distress in resource-poor clinics.

The BLUE protocol standardized the examination sites of the chest, including the upper blue spot, the lower blue spot, the posterior alveolar, and/or pleural syndrome (PLAPS) points on the left and right sides.

First, looking for lung glide sign. If the lung glide sign exists and there is a clear line A, it is called A-profile. Next venous system examination needs to be done. The specificity of diagnosing pulmonary embolism with lower extremity venous thrombosis was 99%. So before other lung areas are examined, veins need to be analyzed. Posterolateral alveolar pleural syndrome (PLAPS) includes posterior chest wall lung consolidations and pleural effusions. PLAPS can be seen for many reasons, and veins need to be prioritized before PLAPS can be found. It has important clinical significance to find lower extremity venous thrombosis after finding A-profile. If no lower extremity venous thrombosis is found, then look for PLAPS at the PLAPS...
examination area. If PLAPS exists, it is called A-no-V-PLAPS image, suggesting pneumonia. Without PLAPS, it is called nude profile (bare image features) (all items are normal), suggesting COPD or asthma. The A’ profile is defined by the presence of A-lines without lung sliding. This profile is seen in pneumothorax. A’ profile requires finding the pulmonary point. If there is a pulmonary point, it strongly suggests pneumothorax. The diagnosis of hemodynamic pulmonary edema is preferred when B features are found. B’ profile (anterior lung B-line without lung sliding), A/B profile (A-line in one hemithorax and the B-line in another hemithorax), and C profile (consolidation of the anterior chest wall) strongly suggest pneumonia. 86% of ARDS patients had one of four pneumonia images.

3.2.6 Monitoring and Guiding Therapeutic Value of Pulmonary Ultrasound

3.2.6.1 Ventilation Score

Since the number and type of ultrasound artifacts (A-line and B-line) seen in the intercostal space of lung ultrasound vary with the loss of pulmonary ventilation function [42], lung collapse or re-expansion can be assessed by tracking the changes in lung ultrasound. In vitro [43] studies have shown that progressive homogeneous ventilation loss determines the transition from A-line to B-line, and the number of B-line gradually increases and fuses. Tissue-like features are present when ventilation is completely lost. Lung ultrasound score (LUS) [44] is a useful tool to quantify the degree of pulmonary ventilation reduction and to compare the degree of improvement of pulmonary ventilation before and after treatment. It realizes the transformation from ultrasound image vectorization to numerical value. According to the axillary front line and the axillary posterior line, the chest wall of the patients was divided into three zones: anterior, lateral, and posterior. The three zones were divided into upper and lower zones, respectively. Thus, one side of the chest wall of the patients was divided into six zones and twelve zones on both sides. Lung ultrasound was performed in each area and scored according to the following criteria: normal pulmonary ventilation (0 points): the presence of lung sliding and horizontal A-lines or no more than two B-lines; moderate pulmonary ventilation reduction (1 point): the presence of multiple uniformly or unevenly segregated B-lines; severe pulmonary ventilation reduction (2 points): multiple rib spaces with combined B-lines; and pulmonary consolidation (3 points): The lungs show tissue-like echoes accompanied by dynamic or static bronchial inflation signs. According to the above criteria, the total score of 12 regions ranges from 0 to 36. Dynamic assessment of LUS can accurately reflect the changes of pulmonary ventilation before and after the implementation of any treatment measures that may affect pulmonary ventilation function thus guiding the next decision-making. Several studies have shown that the clinical value of pulmonary ultrasound in assessing the degree of pulmonary inflation is in good agreement with chest CT. In patients with ARDS, regional
pulmonary ultrasound scores were closely related to tissue density assessed by computed tomography, and the gradual increase in scores from 0 to 3 was significantly related to the increase in density [45].

3.2.6.2 Monitoring the Effectiveness of Antimicrobial Therapy

Lung ultrasound can also be used to evaluate the efficacy of pulmonary infection and can assist in adjusting and stopping antibiotic therapy. The LUS can be calculated by observing regional changes before and after treatment aimed at improving pulmonary ventilation. It has been successfully applied to evaluate antibiotic-induced alveolar reaeration in VAP [46].

3.2.6.3 Monitoring the Extravascular Lung Water (EVLW)

The ultrasound manifestations of EVLW has increased B-line. For acute alveolar or interstitial exudation, increased diffuse B-line can be observed by lung ultrasound. At present, lung ultrasound score can be used for clinical monitoring of EVLW. Baldi et al. [47] evaluated EVLW with B-line score, B-line score correlated well with quantitative CT. The overall LUS was directly correlated with EVLW assessed by pulmonary thermodilution [48], and with the overall lung tissue density assessed by quantitative CT [45]. Increased LUS is an early warning of harmful side effects of fluid resuscitation in sepsis patients, transthoracic lung ultrasound may serve as a safeguard against excessive fluid loading [49]. The LUS is independently related to the 28-day mortality, as well as the APACHE II score and lactate level, in intensive care unit shock patients. A higher elevated LUS on admission is associated with a worse outcome [50].

3.2.6.4 Monitoring Lung Recruitment

Lung reaeration after lung recruitment maneuvers can be monitored by direct and real-time visualization [51]. Bouhemad et al. [52] used LUS to measure the reaeration of PEEP 0–15 cm H₂O in 40 patients with ARDS undergoing mechanical ventilation. The level of pulmonary alveoli (or collapse) was found to be positively correlated with the pressure-volume curve ($P$–$V$ curve). Therefore, ultrasound can assess the potential of lung recruitment, and dynamically monitor and guide the parameter setting of mechanical ventilation. Lung recruitment combined with appropriate PEEP may improve oxygenation and some physiological indexes in ARDS patients, but not in all ARDS patients. The setting of PEEP according to the recruitability of lung can more effectively reopen the collapsed alveoli and reduce the side effects caused by PEEP. Lung ultrasound can synthetically judge the recruitability from the homogeneity, severity, airway patency (dynamic bronchial gas phase), and the presence or absence of tidal recruitment in the examination area. In
the course of recruitment, the response of the lung to different recruitment maneuvers and recruitment time can be assessed by qualitative or semi-quantitative ultrasound scores, and the causes of non-recruitment can be comprehensively analyzed and better treatment strategies can be found [53]. It can also detect the possible barotrauma caused by lung recruitment in time and adjust the treatment in time. It should be noted that pulmonary ultrasound could not detect lung hyperinflation.

### 3.2.6.5 Prone Position

Ultrasound is helpful in evaluating and managing prone position therapy. Pulmonary tissue in gravity-dependent area of ARDS patients in supine position is not easy to reopen due to the influence of gravity, abdominal pressure, and chest motion amplitude. It has been proved that prone position can improve the degree of pulmonary tissue expansion in gravity-dependent areas either alone or in combination with recruitment maneuver thus improve oxygenation and reduce mortality [54].

In the prone position of ARDS patients, ultrasound can assess the lesions or homogeneity of the lungs, and evaluate the lung recruitment in gravity-dependent areas (PLAPS point and posterior blue point in supine position). The degree of dorsal lung recruitment assessed by lung ultrasound after 3 h in prone position was correlated with clinical positive reaction [55]. Therefore, the effectiveness of prone position can be predicted by semi-quantitative ultrasound score, which also can help to determine the time and frequency of prone position.

### 3.2.6.6 Weaning

When mechanical ventilation is disconnected, it will cause significant changes in pulmonary ventilation volume. Ultrasound changes of pulmonary ventilation can predict the success or failure of extubation in patients who successfully passed the 1 h spontaneous breathing test (SBT). There was no significant change in overall pulmonary ventilation during the spontaneous breathing test in patients who succeeded in extubation. However, in patients with post-extubation distress, pulmonary ventilation decreased during the SBT [56].

### 3.2.7 Diaphragm Ultrasound

The diaphragm is an important respiratory muscle. In spontaneous breathing, diaphragm plays an important role in generating tidal volume [57]. Many factors in ICU such as phrenic nerve injury after abdominal or cardiac surgery, neuromuscular disease, mechanical ventilation, sepsis can lead to diaphragm dysfunction, and thus increase the risk of weaning failure and prolong the time of mechanical ventilation [58]. There are some methods of examining diaphragm function, including
electromyography, transdiaphragmatic pressure, X-ray, magnetic resonance imaging, and so on. Most of them are invasive or radioactive examination. Bedside, ultrasound has the advantages of noninvasive, real-time, and highly repeatable. It can not only observe the shape of diaphragm, but also evaluate the function of diaphragm. It has been widely used in clinical diagnosis and treatment of critical care patients.

3.2.8 Measurement

There was no significant difference in the thickness and the change of thickness between the left and right diaphragms. Compared with the left diaphragms, ultrasound could measure the mobility of the right diaphragms more intuitively, and the repeatability of the measurement of the right diaphragms was higher than the left one [59]. Therefore, the liver is often used as an acoustic window to measure the thickness and movement of the right hemidiaphragm. However, when it is suspected that the patient has unilateral diaphragm injury, it is necessary to evaluate the bilateral diaphragm function. For example, in patients undergoing heart surgery, the phrenic nerve injury may cause complete paralysis in half of the diaphragm, while the other part of the diaphragm is not affected, which usually does not cause dysfunction of the whole diaphragm. Therefore, it is necessary to evaluate the function of the two diaphragms separately [60].

3.2.9 Diaphragm Thickness and Change Rate of Diaphragm Thickness

Diaphragmatic thickness refers to the distance between the pleura and peritoneum of the diaphragms at the thoracic involution. When inhaled, the diaphragm contracted and its thickness increased. The change rate of diaphragmatic thickness refers to the change degree of diaphragmatic thickness during respiration, which reflects the contractility of diaphragm [61]. Change rate of diaphragmatic thickness = (maximum end inspiratory diaphragmatic thickness—end expiratory diaphragmatic thickness)/end expiratory diaphragmatic thickness × 100% [62, 63]. In normal conditions, when the lung volume increases from functional residual volume to total lung capacity, the average thickness of diaphragm increases by 54% (range: 42% ~ 78%) [64, 65].

For B-mode ultrasound measurement, select a high-frequency ultrasound probe with a frequency of 7.5 MHz or more, and place it between the axillary front line and the axillary midline between the eighth and tenth intercostals, that is, the junction of the diaphragm and the chest wall. The direction of the probe is perpendicular to the chest wall. Two parallel hyperechoic layers can be seen at a distance of 1.5–3 cm from the skin. The hyperechoic layer near the skin is the pleura layer and
the peritoneal layer at a distance. The area with low echo between the two is the diaphragm [66]. The thickness of diaphragm is the distance between pleura and peritoneum. Using ink to mark the skin to locate the diaphragm can improve the repeatability of measurements. The position of M-mode ultrasound measurement is the same as B-mode. The measurement line was selected after the diaphragm was located by a two-dimensional ultrasound. M-mode ultrasound showed that the thickness of diaphragm changed with the change of respiratory cycle along the measurement line (Fig. 3.14). The measurement of diaphragmatic thickness in more than two respiratory cycles with M-mode ultrasound can improve the repeatability of measurement. The accuracy and repeatability of measurement of diaphragmatic thickness and thickness fraction by ultrasonography have been confirmed [61, 64, 67, 68].

3.2.10 Diaphragm Excursion

Diaphragm excursion refers to the displacement between the inspiratory and expiratory ends of the diaphragm. During the measurement, 3–5 MHz probe is selected, and the patient takes a half-lying position (the head of the bed is raised by 30°–45°). The excursion of different parts of the diaphragm is not exactly the same during the breathing process. The excursion of the middle and rear parts is greater than that of the front part. The measurement of the excursion of the diaphragm is mainly to measure the rear part [69]. Since the amplitude of each breath is different in patients with spontaneous breath, it is necessary to avoid recording very deep or very shallow breath as the evaluation result. It is necessary to measure five respiratory cycles and take their average value as the evaluation result [70].

M-mode ultrasound can continuously record the time-position relationship of the diaphragm on the sampling line and quantify the movement amplitude of the diaphragm. The ultrasound probe was placed at the lower edge of the lower rib between the axillary front line and the clavicular midline to make the ultrasound beam perpendicular to the posterior part of the diaphragm. M-mode ultrasound could show
the excursion of the diaphragm along the sampling line with the breath. When inhaled, the diaphragm moves down close to the probe, and the M-mode ultrasonic track is upward; when exhaled, the diaphragm moves up far away from the probe, and the M-mode ultrasonic track is downward. Phrenic excursion is the vertical distance from baseline to the highest point of the curve (Fig. 3.15). Research shows that the phrenic mobility of healthy volunteers is about 1.0 cm for men and 0.9 cm for women [59, 71].

3.2.11  Contraction Velocity of Diaphragm

M-ultrasound can show the contraction velocity, inspiratory time, and respiratory cycle time of diaphragm (diaphragm contraction velocity = diaphragm mobility/inspiratory time). Diaphragm contraction velocity was related to the muscle strength of diaphragm. Diaphragm contraction velocity was (1.3 ± 0.4) cm/s when the healthy people were breathing peacefully [71].

3.2.12  Application

3.2.12.1  Weaning

The matching of respiratory demand and respiratory muscle strength is the key to the success of weaning. Therefore, diaphragm function is closely related to the success of weaning. Diaphragmatic thickness is helpful to predict the success of weaning, diaphragmatic mobility, and shallow fast breathing index have similar value in predicting the results of weaning [72–74]. Dinino et al. [73] reported that the sensitivity and specificity for predicting the success of weaning were 88% and 71%, respectively, when change rate of diaphragmatic thickness was more than 30%. The results of Ferrari et al. [74] showed that the sensitivity and specificity of the change
rate of diaphragmatic thickness >36% were 82% and 88%, respectively. More studies have reported that the sensitivity and specificity of predicting the results of weaning are better than those of shallow fast respiratory index and maximum inspiratory pressure when the average diaphragm mobility is 1.1 cm. Farghaly et al. [75] found that the diaphragmatic mobility was 16 mm in the successful group and 9.8 mm in the failure group ($P < 0.0001$). The sensitivity and specificity of the successful withdrawal were 87.5% and 71.2%, respectively. At present, most of the studies on diaphragm mobility and change rate of diaphragmatic thickness are observational studies, and a few are case-control studies. Up to now, there is no further randomized controlled trial to determine the time of withdrawal according to diaphragm mobility and change rate of diaphragmatic thickness. Whether it can reduce the failure rate of extubation still needs to be confirmed by further studies [76].

### 3.2.13 Differentiation Between Phrenic Atrophy and Phrenic Paralysis

The main manifestations of phrenic atrophy on M-mode ultrasound are the decrease of diaphragm thickness and motion amplitude [77]. The main manifestation of phrenic paralysis is the contradictory movement of the diaphragm, which can occur in one or both sides of the diaphragm. On M-mode ultrasound, it shows the movement track opposite to the normal diaphragm [78]. Ultrasound can directly observe the thickness, thickening and movement track of bilateral diaphragm to determine whether the diaphragm function is abnormal and the type, so as to provide more useful and reliable information for clinical judgment of the causes of respiratory insufficiency in patients [79, 80].

### 3.2.14 Monitoring Work of Diaphragm

The change rate of diaphragm thickness during mechanical ventilation can reflect the work of diaphragm. Umbrello et al. found that transdiaphragmatic pressure and esophageal pressure were only significantly related to the change rate of diaphragm thickness, but not to diaphragm mobility. Therefore, ultrasonic measurement of the change rate of diaphragm thickness in patients with mechanical ventilation can accurately reflect the work of diaphragm. Monitoring the work of diaphragm can guide the setting of ventilator parameters. Monitoring the thickness of diaphragm by ultrasound, titrating the support level of ventilator parameters, keeping the patient’s inspiratory effort at a normal level, can prevent the change of diaphragm shape during mechanical ventilation. Therefore, monitoring the work of diaphragm by ultrasound can guide clinicians to adjust ventilator parameters.
3.2.15 Evaluation of Synchronization

Simultaneous monitoring of diaphragmatic mobility and airway pressure-time curve of patients under M-mode of ultrasound can evaluate synchronization. This method can help to find out whether there is ineffective trigger in patients, calculate the trigger delay time, and guide clinicians to adjust ventilator parameters and treatment plans. M-mode ultrasound provides a mirror image for the change of esophageal pressure waveform. When inhaled, the esophageal pressure drops, the waveform rises, when exhaled, the esophageal pressure rises, and the waveform declines. Ultrasound can provide the whole process of the beginning and end of inspiration in real-time thus avoiding invasive esophageal pressure monitoring [81]. Therefore, the real-time waveform of diaphragm M-mode ultrasound and mechanical ventilation airway pressure can find the time when the patient triggered the ventilator, and evaluate the synchronization, but further clinical research is needed.

3.3 Electrical Impedance Tomography

3.3.1 Overview

As a clinically available and noninvasive technique, electrical impedance tomography (EIT) has been widely used by clinicians. It can provide dynamic tidal images of gas distribution at the patient’s bedside.

3.3.2 Principle of EIT Imaging

In short, the principle of EIT imaging is based on the difference in pulmonary tissue’s electrical resistance at different phases of respiration. An increased volume of gas in lung tissue increases electrical resistance, while an increased volume of blood or fluid will decrease electrical resistance. While executing EIT, a belt with multiple electrodes is placed around the patient’s chest wall. The number of electrodes varies from 8–32 according to various versions and brands of EIT. Each pair of electrodes emitting very small electrical currents alternately, and the rest electrodes read the voltage generated by the current flowing through the chest. Until a cycle is accomplished, all data needs to build a raw EIT image is acquired, which is called the frame. The EIT ventilation image at this moment can then be displayed according to different imaging methods. Currently, the commonly used imaging technique is based on the change value of the immediate frame and baseline frame, and image frames are usually called relative images. Through these algorithms, a real-time continuous moving image is shown on the screen, enabling clinicians to evaluate patients’ ventilation distribution at the bedside and can also obtain more information through off-line analysis software. The reliability of EIT has been...
confirmed by various common methods, such as CT scan, positron emission tomography, single-photon-emission computed tomography, and pneumotachograph.

The image of EIT is similar to a CT image, which means the anterior side is on the top of the image while the left and the right side is enantiomorphic [82]. The imaging diagram of EIT is shown in Fig. 3.16.

3.3.3 Method of Application

3.3.3.1 How to Place the Belt

The electrode belt should tenderly be placed around the patients’ chest. Although the location of the electrode plane impacts the examinations, there is no consensus on the standard electrode belt position for pulmonary EIT monitoring. In a general way, researchers place the belt at 4–5 intercostal space. We do not recommend placing the belt lower than the sixth intercostal space because the diaphragm may periodically enter the measurement plane [83]. The suitable position of the belt is shown in Fig. 3.17.

3.3.4 Data Directly Obtained on the EIT Instrument

3.3.4.1 Regions of Interest (ROI)

EIT is able to observe pulmonary ventilation in different regions. Regions of interest (ROI) mean different regions obtained by various partition methods. EIT can divide ROI vertically or quadrantally by identifying regions with gas ventilation automatically. Clinicians can also customize the ROI according to ventilation conditions and
needs. Commonly the chest is vertically divided into four parts from top to bottom averagely, among which ROI 1 and ROI 2 represent a non-dependent area while ROI 3 and ROI 4 represent the dependent area. When dividing as quadrants, usually default ROI 1 as the upper left, ROI 2 as the upper right, ROI 3 as the lower left, and ROI as 4 the lower right quadrant. Figure 3.18 shows two common ways of ROI set.

### 3.3.4.2 Functional Image

The functional image represents tidal changes in impedance by a time-series, namely the image observed on the EIT screen that gradually changes with respiration. With gas been inhaled into the lung, the impedance of the lung increases, the lung area on the screen expands. While during the expiration phase the impedance decreases, the lung area gradually darkens and disappears. Through the change of vertical or quadrant ROI, prothorax and dorsal, left and right lung distribution of ventilation can be observed. The functional image of EIT correlates well with CT scan and can evaluate the ventilation heterogeneity conveniently.

### 3.3.4.3 EIT Plethysmogram

EIT plethysmogram is a curve of pulmonary impedance changes accumulated by each breath over a period according to ROI division, containing global and regional data. The change of end-expiratory lung impedance monitored by EIT correlates
well with the change of end-expiratory lung volume monitored through the nitrogen-washout maneuver. Through the EIT plethysmogram, the trend of volume change can be estimated [84].

### 3.3.4.4 Basic Definitions in EIT Measurement

For ease of understanding, the following table lists some common concepts when applying EIT (Table 3.1) [85].

| Region of interest : 4 layers |  | Region of interest : quadrants |  |
|-----------------------------|--|-----------------------------|--|
| 1                           | 8%| 1                           | 27%|
| 2                           | 42%| 2                           | 21%|
| 3                           | 41%| 3                           | 28%|
| 4                           | 9% | 4                           | 20%|

**Fig. 3.18** Regions of interest (ROI). Here a normal EIT image is shown, researchers are able to choose different ROI according to their needs. Gas distribution at each region is expressed as a percentage of global tidal impedance variation.

### 3.3.5 Clinical Application

#### 3.3.5.1 Evaluating Ventilation Heterogeneity

The ventilation status of the lung can be observed directly through the EIT screen. Usually, clinicians divide the lung into the non-dependent area and dependent area as we recommended previously. Under normal circumstances, the gas distribution ratio of these two regions is close to 1:1, while during ARDS or patients with diaphragm paralysis the ratio may increase, with gas accumulation more in the upper
part, due to the change of respiratory system. Traditionally, clinicians adjust the respirator parameter according to the entirety pulmonary condition and respiratory mechanics—improving the collapse of alveoli by means of recruitment maneuver and elevate the PEEP level. However, this method does not reveal the opposite pathology in different parts of the lung, which is that by keeping some of the alveoli open, you may have overinflated another part of the lung. While with EIT, people can identify ventilation differences among different parts of the lung and achieve regional parameters such as regional compliance so that clinical decisions could be adjusted.

### 3.3.5.2 Estimation of Lung Collapse and Overdistension

In 2009, costa et al. proposed the method of using EIT to monitor overextension and collapse of the lung to calculate the optimal peep [84]. They divide the lung into multiple pixels, cooperating decremental PEEP titration after maximally recruiting, and calculate every pixel’s compliance in each PEEP level through formula 1. They search for the best compliance of a certain pixel that appears at a certain PEEP level. They believe that before the best compliance occurs, the alveoli represented by that pixel are overinflated, and after that, the alveoli tend to collapse. In each PEEP level, they calculate the percent of overextension in each pixel(Overextention\_\text{pixel}% \text{)} and the percent of collapse in each pixel(Collapse\_\text{pixel}% \text{)} . They use data acquires before the best compliance appears through formula 2 to calculate Overextention\_\text{pixel}% and

| Name                                    | Definition                                                                 |
|-----------------------------------------|---------------------------------------------------------------------------|
| Baseline                                | Baseline (also called reference), is a reference value to determine electrical impedance variations in time difference EIT. Different choice of baseline has a big impact on impedance calculating and data interpretation. |
| Center of Ventilation (CoV)             | Is used to quantify the distribution of ventilation in relation to vertical or quadrantal ROI division and expressed as percentage. CoV is 50% means there is an equal distribution of gas, in the previous condition, CoV less than 50% means a shift distribution towards dependent area. |
| Change in end-expiratory lung impedance (ΔEELI) | The difference in end-expiratory EIT values between two points of time. |
| Global inhomogeneity index (GI index)   | Means the overall degree of spatial heterogeneity of ventilation.         |
| Pixel                                   | The smallest element in an EIT image and is also the smallest unit in an EIT calculation |
| Regional ventilation delay (RVD)        | RVD quantifies the degree of delay caused by atelectatic area, it measures the delay in the local impedance reaching a particular impedance value, usually up to 40% of the maximum impedance value during a slow inflation maneuver |
| Tidal impedance variation (TIV)         | TIV represents the total impedance change in a breath, the difference between the maximum at the end of inspiration and the minimum at the end of expiration |
use data acquires after the best compliance appears through formula 3 to calculate \( \text{Collapse}_{\text{pixel}} \% \) by the same token. The percent of collapse is set to zero if the best compliance has not been achieved and the percent of overextension is set to zero after the best compliance has already been achieved.

After a weighted average of all pixels’ \( \text{Collapse}_{\text{pixel}} \% \) and \( \text{Overextension}_{\text{pixel}} \% \) in a certain PEEP, through a special algorithm of EIT, they can finally achieve the cumulated percentage of collapse and overextension for the entire lung in a certain PEEP level. Then, according to the various percentage of collapse and overdistension corresponding to different PEEP, the curve of collapse and overdistension with PEEP can be obtained. The collapse of the lung achieved by this kind of PEEP trial following a recruitment maneuver correlates well with the CT method. This idea is also carried on some EIT machines, enabling clinicians to use EIT to calculate the collapse of the lung right after the PEEP trial and choose optimal PEEP conveniently. But people should bear in mind that PEEP which minimizes alveolar overextension and collapse does not necessarily correspond to peep which maximizes overall lung compliance.

\[
\text{Compliance}_{\text{pixel}} = \frac{\text{Local impedance variations}}{(P_{\text{plat}} - \text{PEEP})}
\]

\[
\text{Collapse}_{\text{pixel}} \% = \left( \frac{\text{Best Compliance}_{\text{pixel}} - \text{Current Compliance}_{\text{pixel}}}{\text{Best Compliance}_{\text{pixel}}} \right) \times 100
\]

\[
\text{Overextension}_{\text{pixel}} \% = \left( \frac{\text{Best Compliance}_{\text{pixel}} - \text{Current Compliance}_{\text{pixel}}}{\text{Best Compliance}_{\text{pixel}}} \right) \times 100
\]

### 3.3.5.3 Pendelluft

Traditionally, scholars generally think spontaneous breathing should be encouraged in patients receiving mechanical ventilation, because, on the one hand, it can remain the diaphragmatic muscle’s activity to prevent diaphragmatic disuse and paralysis, on the other hand, keep spontaneous breathing can improve regional ventilation, typically the dependent lung region, help reduce respiratory mechanics parameter and maintain hemodynamic stability. However, in patients with ARDS or a strong contraction of the diaphragm, keeping spontaneous breathing may cause the pendelluft phenomenon. This means at the beginning of inspiration, dependent lung region inflates while non-dependent lung region deflate with no change in tidal volume. In other words, the gas is inspired by non-dependent area to dependent area. This phenomenon was detected and reported by Yoshida through EIT [86]. Pendelluft may cause local atelectrauma in non-dependent area and local volutrauma in dependent area, both of that will worsen lung injury. This phenomenon may concern with the injury lung has less behave of fluid-like behavior and distending pressure conduct unevenly through the pulmonary surface. And right because of the uneven conduction of transpulmonary pressure on the pulmonary surface, the
esophageal pressure cannot represent the entire lung condition. Furthermore, this regional and transitory phenomenon cannot be observed by traditional respiratory mechanics monitoring indicators, while EIT can help clinicians identify such ventilation heterogeneity.

### 3.3.5.4 Pulmonary Perfusion

One of the important objectives of mechanical ventilation is to ensure adequate gas exchange. In addition, to ensure adequate ventilation of the lung, it is also important to ensure adequate pulmonary perfusion. In the article above, we mainly introduced the monitoring and application of EIT in ventilation. In fact, in recent years, the research of using EIT for bedside pulmonary perfusion monitoring has gradually become a hotspot. Both ventilation and blood flow can lead to impedance change which eventually affects EIT monitoring results. This property makes it possible to monitor perfusion by EIT. At present, it is mainly assessed by the “first-pass kinetics” method. The method uses the high conductivity of hypertonic saline as an intravascular contrast agent to help distinguish between pulmonary ventilation and blood flow. Applying this method requires a quick and uniform infusion of 20 mL hypertonic saline through the central venous catheter after a brief pause in inspiration, then the blood signal and ventilation signal will be separated by electrocardiography gating or by algorithms based on the principal component analysis. This method has been confirmed to have a good correlation with electron beam CT, which illustrates EIT is able to detect changes in pulmonary blood flow over time [87].

### 3.3.6 Other Interesting Clinical Applications

Since 2006, clinicians have found that EIT can detect the presence of pneumothorax. In 2017, Morais et al. reported the incidence of pneumothorax on an ARDS patient during recruitment maneuver in detail, which happened to be recorded by EIT [88]. Pneumothorax shows a sudden increase in brightness in the EIT image, and the increase in ventilation is not proportional to the increase in PEEP. Such reports confirm that the EIT is useful in monitoring patients with the need to perform pressure-injury risk procedures.

Chen et al. put forward the airway closure could be underestimated and overlooked. PEEP levels might be set inappropriately because of this phenomenon [89]. Sun et al. published a case report pointing out that using EIT could confirm airway closure. They evaluated global and regional $P-V$ curves, EIT ventilation maps, and plethysmograph waveforms during low-flow inflation, finding that there is a nearly identical infection point on the initial part of both global and regional $P-V$ curves,
meaning that no gas enters the lung at the beginning of the inspiration even in the relatively well-ventilated non-dependent area, which means complete airway closure [90].

### 3.3.7 Advantage of EIT Comparing with CT

Compared to conventional CT, EIT provides bedside, noninvasive, radiation-free, and real-time monitoring, which also provides local information. Applying EIT to ICU patients can avoid the risks associated with transporting patients and may become a more cost-effective option. It is worth noting however that the data provided by the EIT may be relative rather than absolute. Therefore, although EIT is a promising monitoring method, researchers should carefully interpret the data and compare them with the golden standard to maximize the benefits to patients.

### 3.4 Positron Emission Tomography

#### 3.4.1 Introduction

Positron emission tomography (PET) is a functional image technique of nuclear medicine, which detects and measures the gamma rays generated in vivo, then locates and calculates the concentration of radioactive tracer in regions of interest. After analyzing and reconstructing by computer, PET can display the spatial and temporal distribution of the radioactive tracer in the body that will contribute to diagnosing and treatment of diseases, neoplastic disorders in particular [91, 92].

Brownell and Sweet [93] introduced a method to locate the brain tumors with positron emitters in 1953, which was considered as the first successful attempt to apply annihilation radiation in medical imaging. David Kuhl and Roy Edwards had put forward the concept of emission and transmission tomography in the late 1950s. Based on their work, several inchoate tomographic instruments were designed and constructed at the University of Pennsylvania [93]. Michel M.Ter-Pogossian and his colleagues improved tomographic imaging techniques in 1975 [94, 95], they built a system that can detect the “electronic” collimation of annihilation photons by connecting a hexagonal array of receptors to coincidence circuits and then confirmed that the system has a better performance in contrast and resolution than scintillation cameras testing by computer simulation and animal experiment.

After more than half a century of development, PET is widely used in oncology, neuroimaging, cardiology, infectious diseases, pharmacokinetics, musculoskeletal imaging, and small animal imaging. In this section, we will introduce the simple principles and basic concepts of PET and focus on the application and prospect of PET in respiratory function monitoring.
3.4.2 Conception

3.4.2.1 Positron Emission and Gamma Rays

Elements that are constituted by protons (with positive charge), neutrons (with no charge), and electrons (with negative charge) can be represented as $^ZAX$. Z named as atomic number means the number of protons in element $X$ which also equals the number of electrons as long as the nuclei are stable. $A$ was called as atomic mass number in this expression which means the number of protons ($Z$) plus the number of neutrons. The same element has the same atomic number. In other words, for a given element, the number of protons is then determined. In that case, $Z$ can be omitted when $X$ represents a certain element. But a certain element can have different forms that also be called isotopes since the atomic mass number are different.

Proton-rich radioactive nuclei are unstable and need a nuclear change to stabilize itself. It only has two ways to achieve this progress. One is positron ($\beta^+$) decay and another way is electron capture. Positron ($\beta^+$) decay is the process of rearrangement of the nucleus. This transformation reduces a proton and generates a neutron and positive electron (positron) and ejects a neutrino. The positron travels a short distance, interacts with the negative electrons of the surrounding material, loses its mass, and releases two photons moving in opposite directions with equal energy (511 keV) (Fig. 3.19).

The essence of gamma rays, generated by gamma decay is a stream of photons. After the occurrence of $\alpha$ decay, $\beta$ decay, or electron capture, the daughter nucleus is still in an unstable excited state. Then it releases excess energy in the form of gamma photons to reach a stable state. Photons generated from annihilation radiation after the positron decay mentioned above is a kind of gamma rays [96].

Although the principle of PET scan is to use positron decay for imaging, positrons exist for a very short time and have very weak penetration, so they cannot be detected directly. The gamma rays produced by positron annihilation after positron decay can travel through the body and can be detected in PET scan.

3.4.2.2 Radioactive Tracer

Molecule contained radioactive isotope is called radioactive tracer. Because nuclide reactions are more active than chemical reactions, using radioactive tracer to trace atom or molecule is more sensitive, which means the concentration of radioactive tracer can be very low when using in vivo. Substance labeled by isotope do not change its chemical characteristics and biological function thus radioactive tracer absorbing, distribution, metabolism, and excretion within organisms can uncover the function of certain organs. At present, the sources of medical radionuclides are mainly in three aspects: nuclear reactor, cyclotron, and radionuclide generator. The commonly used radioactive tracer in PET scan is labeled by $^{11}$C, $^{13}$N, $^{15}$O, or $^{18}$F (chemical characteristics are similar to H). Those radionuclides are produced from
cyclotron and constitute molecules such as 11CO, 11C methyl albumin, 13N-N2gas, 13N-N2-saline, H215O, C15O, [18F]-fluorodeoxyglucose [97]. Tracer composed of a few other nuclides such as 68Ga-transferrin, 9-(4-[18F]-fluoro-3-hydroxymethylbutyl), and so on are used in PET scan as well to assess pulmonary transcapillary escape rate, gene expression, or other special features.

3.4.3 Applications

Although pulmonary function monitoring is not the primary application field of PET, PET has made some significant contributions in helping to understand respiratory physiology and lung injury mechanism. We will introduce several aspects of the application of PET in lung function monitoring, including ventilation, perfusion, lung vascular permeability, lung water concentration, lung inflammation in ALI and ARDS, enzyme activity, and pulmonary gene expression. At the end of this section, we summarize some limitations of the clinical application of PET.

3.4.3.1 Ventilation and Perfusion

The distribution coefficient (\(\lambda_{\text{water/air}}\)) of nitrogen is 0.015 at 37 °C which means the solubility of nitrogen is very low. When saline containing 13N-N2, injected intravenously, reaches the pulmonary capillaries, nearly all 13N-N2 is converted into a gaseous state and diffuses into the alveoli. Rhodes [98, 99] and his colleagues took advantage of this peculiarity and induced a method using 13N-N2 in saline intravenously at a constant rate to measure regional ventilation-perfusion ratio in 1989, and they calculated that mean ventilation–perfusion ratio of healthy human subjects in the left lung and right lung is 0.8 and 0.76, respectively. This method was modified by Mijailovich [100], Musch [101], and their coworkers. They infused a bolus of saline contains 13N-N2 gas intravenously within 3–5 s and then implemented 30–60 s apnea to make sure radioactive gas was trapped in the lung. After

![Fig. 3.19 A schematic illustration of positron (β+) decay and annihilation of a positron and an electron. Two photons were produced and moving in opposite directions with equal energy (511 keV)](image-url)
breathing is resumed, radioactive gas was washed out as time goes on. When the tracer was injected into the body, continuous PET scanning was performed to obtain the solubility-time curve of radioactive substances in different regions of the lung. When 13N-N2 saline arrived at the lung capillary which located in regions perfused but having no aeration (shunt region), it cannot release 13N2. 13N-N2 saline will flow away with blood thus the tracer activity will get to an early peak and decline gradually to a plateau during the apnea period. Radioactive tracer cannot arrive at lung region which is not perfused since there is no blood flow. If the perfusion of the region of interest is impaired, the tracer activity will decrease during the period of apnea compared with normal perfusion regions. In some situations, for example, air trapping occurring in asthma or chronic obstructive pulmonary disease, 13N-N2 dissolve in saline change into gas stage when it arrives at the lung capillary during apnea, but on account of no or poor gas exchange, 13N-N2 in gas stage was retained in lung and tracer activity decrease slower than normal gas exchange lung region during the washout period. Investigator proposed a mathematical model to determine the distributions of pulmonary perfusion, ventilation, and shunt and verify the model is accurate in normal animals and acute lung injure animals [102, 103]. Musch and coworkers [101] found that both perfusion and ventilation tend to distribute to dependent regions either in supine position or in prone position in healthy humans with PET scan and 13N-N2 saline bolus technique. Using PET scan and 13N-N2 saline bolus injection technique, they also identified redistribution of perfusion toward collapse regions which may be the reason for the worsening of oxygenation that occurred with sustained inflation or high PEEP [104, 105].

However, with the infusion of 13N-N2, it is not feasible to quantify the ventilation regions poorly perfused thus methods ground on analyzing the kinetics of inhaled tracer are put forward. An inhaled 13N-N2 PET scan was used to measure regional alveolar volume and ventilation in experimental acute lung injury animals to explain the pathophysiology progress of ventilator-induced lung injury [106]. Regional specific volume change (sVol), defined as the ratio of regional tidal volume and regional end-expiratory (EE) gas volume, is another important variable in the mechanism of ventilator-induced injury. sVol associated with tidal volume and lung strain can provide information on the estimation of elastance and ventilation regionally. Tyler J.Wellman and colleagues used 13N-N2 inhaled and washout technique and respiratory-gated PET to assess regional lung expansion [107].

Intravenous injection or inhalation of 13N-N2 can be used to assess regional ventilation, perfusion, shunt, and gas trapping, but, since the need for on-site cyclotrons to produce 13N2, the application of those methods is limited. 68Gallium generated at the PET facility needs no on-site cyclotrons and can be chelated to numerous functional molecules for imaging in PET scan. Hnatowich DJ, Chesler DA, and their group first used 68Gallium in lung image to gain lung perfusion tomography by injecting radioactive albumin microspheres in dogs [108, 109]. It has been proved that PET scan with 68Ga labeled tracer has higher-resolution and more capacity in regional quantitation of lung function compared with conventional ventilation-perfusion ratio imaging (SPECT/CT) in diagnosing patients with suspected pulmonary embolism [110]. In the evaluation of airways disease, PET scan with Galli-gas provides more information in ventilation distribution and has better
performance in differentiating ventilation heterogeneity compared with SPECT with Techne-gas, and this method is expected to be applied in small airways disease [111]. Another study using PET scan with 68Ga labeled albumin aggregates gain an insight into the pathogenesis of ARDS in experimental rats [112]. Investigator has shown that perfusion of regions affected by acid aspiration was increased within 10 min as a result of hyperemic responses and was decreased, as early as 2 h, explained by hypoxic pulmonary vasoconstriction or direct compression of vessels by exudate.

Schuster and coworkers found that the fraction of pulmonary blood flow (PBF) to dependent regions increased while the PaO$_2$/FiO$_2$ ratio decreased by measuring regional pulmonary perfusion with H215O in acute lung injury (ALI) patients [113]. Their group also found that the main mechanism of perfusion redistribution to aerated regions rather than flooded alveoli was hypoxic pulmonary vasoconstriction [114].

In summary, with the help of PET scan, a physician can measure global and regional ventilation, perfusion, and ventilation–perfusion ratio, that may make contribution to identifying the presence of pulmonary embolism, assess lung function before radiotherapy, predict lung function after pneumonectomy, evacuate the severity of chronic obstructive pulmonary disease (COPD) and asthma, and understand the mechanism of ALI, VILI, and ARDS.

### 3.4.3.2 Lung Vascular Permeability and Lung Water Concentration

In 1987, Mark A. Mintun [115] and coworker proved that PET was useful in evaluating vascular permeability changes in acute lung injury experimental animals and patients. They calculated a new index, pulmonary transcapillary escape rate (PTCER), which describes the movement of 68Gallium transferrin from pulmonary vascular to extravascular in dogs repeatedly, and found that there was no significant change of the new index. They also tested it in healthy human volunteers and patients with acute respiratory distress syndrome (ARDS) and showed that the difference of PTCER in normal volunteers and patients with ARDS was similar in an animal model. PET methods can be a substitute for protein flux measurements for evaluating pulmonary vascular permeability accurately. Lung water concentration (LWC) can be assessed accurately and reproducibly by PET with 15O labeled water in supine dog, Velazquez.M [116] and coworkers found an excellent linear correlation between regional LWC measured gravimetrically and regional LWC measured by PET ($r = 0.92$).

### 3.4.3.3 Lung Inflammation in ALI and ARDS

PET imaging is used in the assessment of inflammation of acute lung injury and acute respiratory distress syndrome as a result of the development of tracer related to the inflammatory response. 2-[18F]fluoro-2-deoxy-D-glucose ([18F]FDG), the most common radioactive tracer applied in PET imaging of
lung inflammation, is transported into cells and transformed into FDG-6-
phosphate. The FDG-6-phosphate is trapped in cells temporarily which cannot
be metabolized further. PET imaging finished before radioactive tracer is
extruded from the cell and filtered by the glomerulus, excreted in the urine
eventually. [18F]-FDG is initially used in diagnosing and staging of neoplastic
disease, recently it has been used in evaluating lung inflammation. In 2004,
Heather A. Jacene [117] and coworkers reported a case of increased [18F]-FDG
uptake in pulmonary with acute respiratory distress syndrome patients. They
assumed that inflammatory cells involved with the pathogenesis of ARDS uti-
лизed glucose at a high rate compared with normal tissue cells, which may
explain the phenomenon of increased pulmonary [18F]-FDG uptake they
observed. It was proved that the rate of [18F]-FDG uptake was associated with
the state of neutrophil activation which made PET scan with [18F]-FDG a use-
ful tool to understand neutrophil kinetics in the pathophysiological process of
ALI. Delphine L. Chen [118] observed a similar phenomenon in ALI dogs.
They also came up with a method to estimate the rate of [18F]-FDG uptake in
the lungs during ALI which was testified by comparing tracer activity derived
by PET and blood time-activity data as the gold standard. With those work as
the cornerstone, [18F]-FDG PTE imaging can be applied in the following clin-
ical scenarios. If critically ill patients have an increased [18F]-FDG activity in
the lungs, the differential diagnosis should include ARDS, this may help to
screen ARDS patients early. In another aspect, PET scan with [18F]-FDG is
used in quantifying the anti-inflammatory therapies response and assessing the
efficacy of novel anti-inflammatory drugs. It also can help to understand the
mechanism of ARDS and instruct ventilator parameter settings. It provides
visualized evidence that regions with normal aeration on CT scan also affect by
lung inflammation. Moreover, the higher plateau pressure (often above
27 cmH2O) and larger dynamic strain it is, the worse inflammation occurred.
These results suggest that for ARDS patients, the tidal volume setting should
be relatively small, so as to avoid barotrauma and reduce the inflammatory
response [119, 120].

3.4.3.4 Enzyme Activity

Vascular remodeling is one of the most important mechanisms of primary pulmo-
nary hypertension (PPH). The expression of factors, such as angiotensin-converting
enzyme (ACE), which may promote vascular remodeling is increased in the region
of active remodeling. Many studies have found that the expression of ACE increases
in patients with PPH or pulmonary hypertension experimental animals. PET imag-
ing with [18F]-fluoro-captopril has been developed to evaluate lung ACE expres-
sion in experimental animals and humans. This method also is used in evaluating the
efficacy of ACEI in the treatment of PPH which can attenuate pulmonary hyperten-
sion and slow down vascular remodeling [121].
3.4.3.5 Pulmonary Gene Expression

PET reporter gene (PRG) imaging is based on the principle of introducing reporter genes into specific tissues with the help of modern molecular biology methods, the products of which trap radioactive tracers, also called PET reporter probe (PRP), then the PET instrumentation detect the signal generated by PRP, located where the reporter genes express. Herpes simplex virus (HSV) type I thymidine kinase (mHSV1-tk) is one of the most common PET reporter genes used in lungs, and 9-(4-[18F]-fluoro-3-hydroxymethylbutyl) guanine ([18F]FHBG) is used as the PRP. With this technique, it is possible to monitor the effect of transgene therapy in the lungs.

3.4.4 Limitation of Clinical Application of PET

All methods mentioned above share the same inherent limitations of PET. First of all, PET scan requires sophisticated and bulky instruments, as well as extremely high radiation protection requirements, which is almost impossible to be carried out bedside. PET is not suitable for critically ill patients who are difficult to go out for examination. Secondly, because of the complex preparation process of most radioactive tracer, the cost of PET scan is still very high. Many technologies are still in the research stage and cannot be extended to clinical practice. Third, PET scan has a low anatomical resolution, and it often requires CT or MRI scan synchronously to locate lesions accurately.

3.4.5 Perspectives

With the development of molecular imaging, PET scan is playing an increasingly important role in this field. With the help of molecular imaging with PET, the understanding of the imaging changes of diseases has developed from the organ or tissue level to the cellular or molecular level. Therefore, it is expected that diagnosis can be made at the beginning of the disease before it reaches an irreversible state, subsequently gaining an opportunity for the treatment of diseases. Another development of PET scan is equipment upgrading and algorithm optimization of image reconstruction. At present, most PET devices are hybrid and multimodal, which also can perform CT or MRI imaging. In future, the hybridization PET scan will have further development in developing devices with closer functional integration, higher signal quality, and faster imaging speed.
3.5 Magnetic Resonance Imaging

3.5.1 Introduction

Magnetic resonance imaging (MRI) is a form of tomography that uses magnetic resonance (MR) to extract electromagnetic signals from the body and reconstruct information about the body. Like PET and SPECT, MRI is also a form of emission tomography, signals of which used for imaging come directly from the object itself with no need for radioactive isotopes, that makes MRI safer. A radio-frequency pulse of a certain frequency was applied to the body in a static magnetic field, then hydrogen protons in the body were stimulated as a result of magnetic resonance. After the pulse is stopped, the proton generates an MR signal in the relaxation process. Image is generated through MR signal reception, spatial coding, and image reconstruction.

3.5.2 Brief History

Felix Bloch from Stanford University and Edward Purcell from Harvard University independently discovered the phenomenon of magnetic resonance in 1946; hence, they shared the Nobel Prize in physics in 1950. Shortly after the discovery of MR, scientists discovered that hydrogen atoms in water molecules can generate MR, which could be used to obtain information about the distribution of water molecules in the human body and thus accurately map the internal structure of the human body. Based on this theory, scientists succeeded in distinguishing cancer cells from normal tissue in mice by measuring the relaxation time of the MR. In 1972, Paul Lauterbur developed a set of spatial coding methods for MR signals, which could reconstruct the image of the human body. After that, MRI technology became more and more mature and applied in a wide range, becoming a routine medical detection method.

3.5.3 Image-Forming Principle

Nucleons with odd numbers of protons or neutrons, such as 1H, 19FT, and 31P, have an intrinsic property: spin. Normally, the arrangement of nuclear spin axes is irregular, but when placed in an external magnetic field, the spatial orientation of nuclear spin makes a transition from disorder to order. The magnetization vector of the spin system increases gradually, and when the system reaches equilibrium, the magnetization reaches a stable value. If the nuclear spin system is affected by external factors such as a certain frequency of radio-frequency pulse can cause a resonance effect. After the radio-frequency pulse stops, the excited nucleus of the spin system
cannot maintain this state and will revert to the original arrangement state in the magnetic field. At the same time, it will release weak energy which will convert into a radio signal. The signal is detected and analyzed to obtain the image of nuclear distribution in motion. The process by which the nuclei return from an excited state to an equilibrium arrangement is called relaxation. The time it takes is called relaxation time. There are two kinds of relaxation time, T1 and T2. T1 is the spin-lattice or longitudinal relaxation time and T2 is the spin-spin or transverse relaxation time [122].

The most commonly used nucleus for MRI is the hydrogen proton, because it has the strongest signal and widely present in human tissues. There are many factors which include proton density, length of relaxation time, the flow of blood and cerebrospinal fluid, paramagnetic substance, and protein can affect MRI imaging. Another characteristic of MRI is that flowing liquid does not produce a signal called flowing void effect. This makes it possible to separate the pipe network in the body, such as blood vessels and the biliary tract, from the soft tissue.

### 3.5.4 Classification of MRI

MRI can be divided into plain scan and enhanced scan according to whether the contrast agent is used or not. Plain scan means scanning without contrast agent and enhanced scan use contrast agent in scanning. By injecting an MRI contrast agent, the resonance time of tissues under an external magnetic field can be shortened, the difference of contrast signals can be increased, and the clarity of imaging can be improved. Depending on the purpose of examination, MRI can be divided into Magnetic Resonance Angiography (MRA), Magnetic Resonance Cholangiopancreatography (MRCP), Magnetic Resonance Urography (MRU), Magnetic Resonance Myelography (MRM), and so on.

### 3.5.5 Contrast Agent of MRI

MRI contrast agents can be divided into longitudinal relaxation contrast agent (T1 preparations) and transverse relaxation contrast agent (T2 preparations). T1 preparations use paramagnetic metal ions to directly affect hydrogen ions in water molecules to shorten T1 thus enhancing the signal and making the image brighter; T2 preparations are used to shorten T2 by interfering with the inhomogeneity of the external local magnetic environment thus weakening the signal and darkening the image. According to the magnetic composition, MRI contrast agents can be divided into three categories: paramagnetism, ferromagnetism, and superparamagnetism. The most commonly used paramagnetic contrast agents in clinical practice are Gadolinium contrast agents.
3.5.6 Application

MRI is widely used for the diagnosis of various diseases especially in the brain, spinal cord, large blood vessels of the heart, joint bones, soft tissue, and pelvic cavity, due to its features of non-radiation, high resolution of soft tissue, and flowing void effect. However, due to the characteristics of MRI scanning technology and the characteristics of the lung itself, the application of MRI in lung diseases is not as usual as others. One of the reasons is that the time required for MRI scanning is relatively long. As a result of the respiratory movement, imaging is often unsatisfactory when there is no suitable contrast agent. Scanning under the condition of breath-holding methods requires well cooperation of the patients, which is more impossible in critically ill patients. Another reason for limiting the clinical application of pulmonary MRI is that the proton density in lung tissues is only one-fifth of that in other solid organs, which is not enough to generate sufficient signals to achieve a satisfactory resolution. However, due to the development of contrast agents and the improvement of imaging speed, MRI is expected to be a radiation-free alternative to CT.

3.5.7 Structural Image

In the field of pulmonary structure imaging by MRI, pulmonary angiography is expected to be widely used. In earlier studies, pulmonary angiography was mainly performed by injecting Gadolinium-enhanced contrast agents to obtain images with satisfactory spatial resolution. However, in recent years, due to increasing concerns about the safety of Gadolinium-enhanced contrast agents, researchers hope to investigate a technology that can perform pulmonary angiography without the need for contrast agents. MRI’s unique flowing void effect makes it possible. Balanced steady-state free precession (SSFP) has been considered as a preferent pulse sequence strategy for a long time in pulmonary angiography. Based on SSFP, Bieri [123] and his coworkers proposed ultrafast SSFP pulse sequences, making 3D-MRI pulmonary angiography without contrast agents possible. Bieri reports a case that the reconstructed image has almost no artifact or degradation caused by balanced SSFP. Morphological lung imaging with high spatial resolution and high contrast-to-noise ratio can be obtained using this method mentioned before, which allows visualization of lung parenchyma and airspaces even in inspiration. Another pulse sequence used to acquire a high quality of lung MR image is ultrashort echo-time (UTE) technology. With the assistance of imaging navigator system or respiratory bellows signal to synchronize 3D image acquisition with the respiratory cycle, the UTE acquisition can generate 3D images of the lung in whole with unprecedented spatial resolution and signal-to-noise ratio. Johnson KM [124] and his coworkers used UTE acquisition to obtain images of airway walls, lobar fissures, and other structural features in free-breathing volunteers and patients, which is not exemplary.
seen in normal lung MRI. MRI is also used in assessing diaphragmatic motion during inspiration and expiration with satisfied spatial and temporal resolution. MRI has been proved to be a useful method to assess diaphragm movement in COPD patients, and it may play a role in evacuating diaphragm dysfunction in patients undergoing mechanical ventilation. With these advances in pulmonary structural MRI, it is possible to reveal the mechanism ventilator-associated lung injury and changes in pulmonary structures during disease progression in patients with ARDS, which will contribute to the early diagnosis, stratification, and individualized treatment of ARDS patients.

3.5.8 Functional Image

MRI is an effective tool to study pulmonary functions, of which ventilation and perfusion are the two research hotspots. Previous studies have shown that pulmonary ventilation and perfusion are distributed by gravity gradients in healthy individuals. In pathological conditions, lung ventilation and perfusion are redistributed as a result of regulatory mechanisms to compensate for impaired lung function, meet the body’s need for oxygen, and eliminate more carbon dioxide produced by metabolism. Measurement of pulmonary ventilation and perfusion, both global and local, is helpful to have a better understanding of the development of pulmonary diseases and therapeutic reactivity.

The first ventilation MRI was performed in 1994 [125], which was implemented by using hyperpolarized 129Xe. 129Xe is gradually replaced by 3He since the latter is easier to polarize. Oxygen-enhanced MRI is another technique used to visualize pulmonary ventilation. It has been confirmed that pulmonary ventilation assesses by hyperpolarized gas MRI is feasible and reliable [126]. The extent of pulmonary ventilation measured by hyperpolarized gas MRI has a good correlation with the measurement results of spirometry. In patients with asthma or COPD, hyperpolarized gas MRI can be used to detect airway obstruction with sensitivity and specificity no less than that of high-resolution CT, which may potentially apply in ARDS patients in the future. High temporal resolution images can be obtained by MRI scanning with gated image acquisition technology, which can show the distribution of ventilation dynamically during continuous breathing, which will make it possible to assess the severity and range of air trapping directly. Thus, dynamic ventilation MRI is going to play an increasingly important role in various obstructive lung diseases since it is quantitative and is no need to expose to radiation.

Unlike 3He, 129Xe is not only existed in the pulmonary gas spaces but also can spread across the blood-gas barrier which makes evaluation of gas exchange quantitatively possible. Hyperpolarized gas MRI with 129Xe can provide information about gas exchange parameters which includes alveolar surface area, septal thickness, and vascular transit time [127]. Hyperpolarized gas MRI is also potentially applied in guiding the mechanical ventilation parameter setting. McGee KP [128] and his coworkers compared the parenchymal elasticity in normal and edematous,
ventilator-injured lung by magnetic resonance elastography (MRE). Their results showed that lung elasticity in animals with regional lung injury decreased compared with normal animals, and in the presence of alveolar flooding, there was no correlation between airway pressure and pressure of the lung parenchyma. Therefore, they cautioned that, unlike conventional pressure-volume approaches, MRE evaluates lung function on the topographical distribution of injury rather than considering the lung as a whole. Maurizio Cereda [129] and his group used 3He MRI as a tool to assess the effect of PEEP on alveolar recruitment and atelectasis-induced hyperinflation in rats ongoing mechanical ventilation and their studies concluded that measuring regional respiratory gas diffusivity by hyperpolarized gas contrast MRI was a potential method to optimize the effects of parameters settings during mechanical ventilation. An animal study [130] reported in 2016 demonstrated that MRI could detect tiny areas of ventilator-induced injury earlier than significant lung injury occurs, which makes MRI a possible research tool to observe the occurrence and development of VILI and the therapeutic effect of protective mechanical ventilation on ALI in real-time. This further understanding of the pathophysiological mechanism during lung injury has attracted attention to the heterogeneity of lung injury and individual variation in response to treatment, leading to the trend of individualized treatment in clinical mechanical ventilation.

Another important aspect of lung function is perfusion. There are two main MR techniques, one of which is a contrast-enhanced MR perfusion image, another is arterial spin labeling (ASL), to assessed pulmonary perfusion. The contrast-enhanced MR perfusion image is performed as follows. A gadolinium-based paramagnetic contrast agent is injected into vein and then a gradient-echo pulse sequence is initiated. The collected signals are integrated and calculated to provide qualitative and quantitative parameters about pulmonary perfusions, such as transit time, volume, and flow of lung blood. However, as mentioned above, non-contrast-enhanced MR perfusion image gradually replaced contrast-enhanced MR perfusion image due to increasing concerns about the safety of contrast agents and the desire for noninvasive examination in a partial patient such as children. With the improvement of MR technologies, limitations of non-contrast-enhanced MR perfusion image such as long acquisition times and artifacts due to motion have been overcome. ASL uses MR-tagged water in blood excited by an inversion pulse as an endogenous contrast agent to generate sensitivity of lung blood flow. Pulmonary perfusion MRI was mainly used in diagnosis and stratification of pulmonary embolism, COPD, asthma, pulmonary cystic fibrosis, and malignant tumor. Researchers integrate pulmonary ventilation and perfusion into a comprehensive index known as ventilation–perfusion (V/Q) ratio since ventilation-perfusion mismatch is a common pathophysiological cause of refractory hypoxemia. There are three main MRI techniques used to measure global and regional ventilation–perfusion ratio: ASL-FAIRER, oxygen-enhanced MRI, and fast gradient-echo with multiple short TE. However, compared with CT and PET, few studies have been reported to evaluate the pulmonary ventilation–perfusion ratio in critically ill patients who needs mechanical ventilation, possibly because the MRI-compatible ventilator is not widely used in clinical practice.
3.5.9 **Perspective**

With the development of MRI equipment and techniques, newer signal acquisition systems permitting fewer measurements are required to reconstruct entire 3D images, leading to an improved image examinations since MRI is convenient and less invasive. Thanks to the promotion of the MRI-compatible ventilator, it is reasonable to believe that MRI plays an important role in visualizing and quantifying the pulmonary structural and functional changes in patients with mechanical ventilation. According to a clinical review [131], it is inferred that MRI can detect the morphological and pathophysiologival patterns (such as “ground-glass opacification” or “consolidation” found by CT) in ARDS patients. Hybrid imaging would be another area in which MRI may play an important role in the future. Inspired by the successful combination of PET and CT, the combination of PET and MRI is an attractive challenge [132]. The high soft-tissue contrast MRI can make up for the low spatial resolution of PET and PET/MRI can reduce exposure to ionizing radiation compared with PET/CT, those advantage of PET/MRI may be useful in assessing structural or functional changes of the lung in mechanically ventilated patients.

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