

Principles of respiratory investigation

Introduction



Key points

- A detailed clinical history should always be the first step in making a diagnosis.
- Physical examination provides crucial clues to guide more advanced diagnostic procedures.
- Microbiological, histological and cytological laboratory tests can diagnose or rule out a large number of diseases.
- Respiratory function testing enables assessment of severity and monitoring of treatment, as well as giving diagnostic information.
- A range of radiographic and other imaging techniques permit physicians to visualise problems within the chest, and can be used to guide more invasive investigations.

Respiratory diseases are of multiple origin, as detailed in the previous chapters of this book. Diagnosis and follow-up often requires various investigative procedures, which should be applied in an appropriate and cost-effective step-by-step evaluation.

History

Taking a careful clinical history is always the first diagnostic step and is an essential approach to the patient. Specific respiratory symptoms include dyspnoea, abnormal breath sounds (such as wheezing or stridor), hoarseness, cough with or without sputum production, haemoptysis, snoring and chest pain. Each may be of different onset (acute or chronic) or severity, isolated or combined, and sometimes accompanied by general symptoms of disease such as fever, weight loss, oedema, night sweats, nocturia or daytime somnolence.

For some disease areas, additional specific questionnaires can be helpful; for example, in allergic or occupational diseases or suspected sleep apnoea.

Often, the clinical history provides – or at least suggests – the diagnosis prior to investigation.

“

Taking a careful clinical history is always the first diagnostic step and is an essential approach to the patient

”

Physical examination

Physical examination classically follows a sequence: inspection, palpation (feeling with the hands), percussion and auscultation (listening with a stethoscope). Inspection may show important physical signs such as cyanosis, abnormal breathing patterns, finger clubbing, chest wall deformities, oedema, superior vena cava syndrome or Horner's syndrome. Palpation may detect, for instance, enlarged lymph nodes, subcutaneous emphysema or points of tenderness. Percussion may reveal areas of dullness (e.g. pleural effusion) or hyperresonance (e.g. pneumothorax) and auscultation may detect abnormal breath sounds, such as wheezes, crackles, or a pleural friction rub, signs that are characteristic of particular respiratory diseases.

The clinical history and physical examination provide the essential clues towards the possible underlying respiratory disease, guiding selection of the appropriate diagnostic investigations: laboratory tests, respiratory function tests, imaging techniques and/or biopsy procedures.

Laboratory methods

Besides routine laboratory blood and urine tests, several specific blood and other tests for respiratory diseases are available (table 1). Investigations of sputum include bacteriological examination, cell differentiation, including eosinophils, and measurement of various inflammatory mediators. Exhaled gases or exhaled breath condensates, such as carbon monoxide and exhaled nitric oxide fraction, are used as markers of inflammatory and other diseases.

Microbiological tests

Microbiological tests have an essential role in the investigation of infectious respiratory diseases caused by viruses, bacteria, fungi or parasites. They include examination of expectorated (or induced) sputum and of specimens acquired by invasive biopsy techniques

(discussed further later). The standard bacteriological techniques of microscopy and culture are often supplemented by molecular biological techniques (PCR) for detecting the DNA (or RNA) of the organism. Testing the susceptibility to antimicrobial agents is clinically very important.

Serological tests for confirming particular infections include identification of the relevant bacteriological or virological antigens and measurement of specific antibodies, in particular the demonstration of a rise in antibody titre. Urinary antigen detection may permit the rapid diagnosis of pneumococcal and Legionella infections.

Respiratory viruses may be cultured from different materials, most easily from nose or throat swabs. Serological tests in general provide only a retrospective assessment; specific immunoglobulin M may be of greater diagnostic value.

The laboratory diagnosis of pulmonary fungal infections is usually based on isolation of the organism from cultures, histological examination and serological tests, but also on direct microscopy after special staining (e.g. *Pneumocystis jirovecii*).

Parasitic lung infections may be detected by microscopy of certain materials (e.g. stool, blood), serological tests or histological tests.

Disease	Test
Pulmonary embolism	D-dimer
Inherited emphysema	α_1 -antitrypsin
Cystic fibrosis	Specific genetic tests
Lung cancer	Tumour marker (e.g. CEA, CYFRA 21-1, NSE, SCC)
Malignant mesothelioma	Tumour marker (mesothelin, osteopontin, fibulin)
Pneumonia	Procalcitonin
(Latent) tuberculosis infection	Tuberculin skin test, interferon-gamma release assays
Unexplained breathlessness	NT-proBNP (increased in heart failure)
Sarcoidosis	Angiotensin-converting enzyme (ACE)
Extrinsic allergic alveolitis (hypersensitivity pneumonitis)	Specific precipitating antibodies
Asthma	Total and specific immunoglobulin E, skin testing with allergens
Eosinophilic diseases	Eosinophils
Connective tissue disorders	Immunological tests such as rheumatoid factor
Pleural effusion	Total protein, LDH, glucose, cholesterol and others in pleural fluid

Table 1 – Specific laboratory tests for some respiratory diseases. NT-proBNP: N-terminal pro-brain natriuretic peptide; LDH: lactate dehydrogenase.

Histological and cytological examination

Histology and cytology play a central role in the diagnosis of many malignant and benign respiratory diseases, including infections. Apart from expectorated sputum, which can be examined cytologically, the specimens are acquired using various biopsy techniques (discussed further later) and are sent for histological and/or cytological evaluation.

Conventional histopathological techniques are often supplemented by immunohistochemistry using specific markers for the differentiation of several neoplasms, such as small cell neuroendocrine carcinoma and malignant lymphoma. In addition, results from molecular diagnostic tests may have important therapeutic ('targeted' treatment) as well as prognostic implications in certain types of nonsmall cell lung cancers (e.g. if mutations of the epidermal growth factor receptor (EGFR) are present).

Cytopathological examination is used mainly in the diagnosis of malignancies (e.g. malignant effusion). In bronchoalveolar lavage fluid, it may be helpful in the diagnosis of some interstitial lung diseases, such as extrinsic allergic alveolitis (hypersensitivity pneumonitis), eosinophilic pneumonia, alveolar proteinosis or asbestosis.

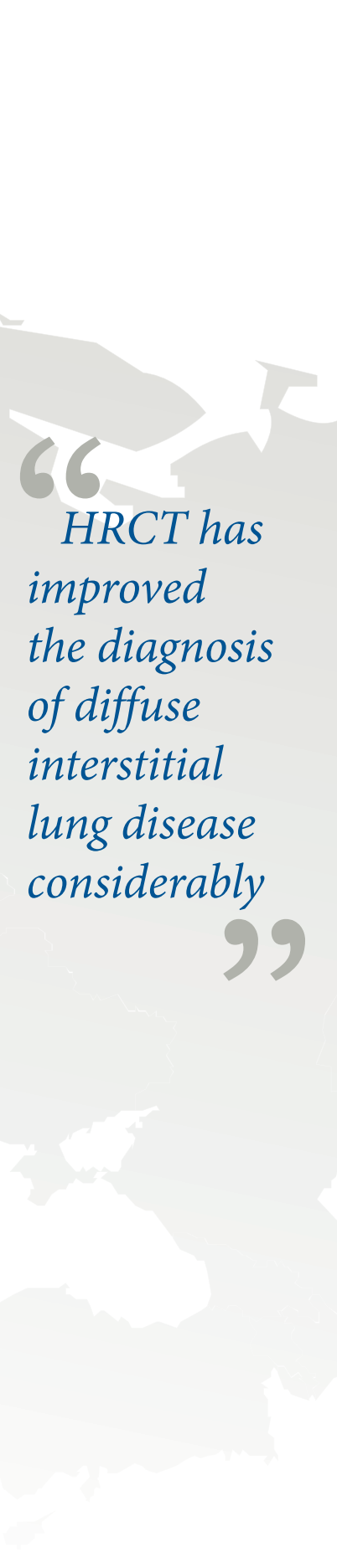
Ultimately, autopsy examination of the lung may provide important information regarding the underlying disease, but it is rarely performed nowadays.

Respiratory function tests

The main clinical roles of respiratory function tests include diagnosis, assessment of severity, monitoring treatment and evaluation of prognosis.



Figure 1 – a) Patient performing spirometry. b) Interpretation of spirometric curves. Reproduced from GARBE, 2010.



“HRCT has improved the diagnosis of diffuse interstitial lung disease considerably”

Spirometry

Spirometry (figure 1) is the most important function test – it measures vital capacity (VC) and forced expiratory volume in 1 second (FEV₁). This permits differentiation between restrictive and obstructive respiratory diseases. If expired volume is measured by electrical integration of airflow (using a pneumotachograph), maximum flow–volume curves can also be registered. These tests are used to measure the effect of bronchodilating drugs on reversibility of obstruction as well as to determine responsiveness to bronchial provocation tests. Simple instruments for patient home use include peak flow meters, which measure the degree of obstruction.

Lung capacity and airway resistance

The total lung capacity can be determined using either gas dilution techniques or body plethysmography. The latter method also allows the measurement of airway resistance. The forced oscillation technique, which measures the resistance of the total respiratory system, has the advantage that the patient does not need to perform specific breathing manoeuvres.

Diffusing capacity

The diffusing capacity of the lung for carbon monoxide (also known as transfer factor), which is usually performed as a single-breath test, measures the overall gas-exchange function of the lung.

Blood gas analysis

Arterial blood gas (ABG) measurement to determine the arterial oxygen tension (P_{aO_2}) and arterial carbon dioxide tension (P_{aCO_2}) is one of the most useful diagnostic tests: blood can be sampled directly from an artery, or an estimate can be obtained from capillary blood from, for instance, a warmed earlobe. ABG measurement allows the diagnosis of hypoxaemia (decreased P_{aO_2}) with or without hypercapnia (increased P_{aCO_2}), a sensitive index of inefficient pulmonary gas exchange, which is also used for defining respiratory failure. P_{aO_2} measurement after breathing 100% oxygen is sometimes used to estimate the anatomical right-to-left shunt. Arterial oxygen saturation (S_{aO_2}) represents the percentage of binding sites on the haemoglobin molecule occupied by oxygen and offers a noninvasive method of estimating arterial blood oxygenation; it is measured directly by an oximeter with a probe attached to either the finger or the earlobe. P_{aCO_2} can also be estimated noninvasively, using a transcutaneous electrode but such devices are not yet as widely used as oximeters. ABG measurement also allows evaluation of acid–base disorders.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET), with determination of minute ventilation, cardiac and respiratory frequency, oxygen uptake and carbon dioxide output, is an objective measure of exercise capacity (spiroergometry). Simpler tests use capillary oxygen partial pressure measurements during exercise on an ergometer or symptom-limited walking tests, such as the 6-min shuttle walk test, with measurement of SaO₂ using an oximeter.

Respiratory muscle function measurement

Respiratory muscle function is commonly assessed by measuring maximal pressures generated at the mouth during maximal inspiratory and expiratory efforts against an occluded airway.

Control of ventilation

Tests of ventilatory control include the hyperoxic rebreathing method and the hypoxia-withdrawal method. Simpler, but less specific, is the measurement of the mouth occlusion pressure.

Diagnosis of sleep breathing disorders

The diagnosis of sleep-related respiratory disorders requires special tests. The gold standard is polysomnography, but simpler tests are available for screening purposes ('respiratory polysomnography').

Right heart catheterisation

Right heart catheterisation is used in the differential diagnosis of pulmonary hypertension.

Intensive care monitoring

The management of respiratory failure in the intensive care unit requires, in addition to frequent checking of ABGs, the measurement of several special parameters (e.g. tidal volume, inspiratory and expiratory pressures); in mechanically ventilated patients, these are often measured automatically by the ventilator.

Imaging techniques

Chest radiography

Chest radiography (X-ray) is an essential part of the diagnostic (and monitoring) examination, and is the first step in the radiological evaluation of patients with suspected respiratory diseases. Modern digital radiography offers a high image quality and the potential for reduction of the radiation dose.

Computed tomography

Computed tomography (CT) of the chest is the second most important radiological modality in respiratory medicine, allowing much more detailed visualisation of thoracic structures than radiography. It is often performed with intravenous contrast

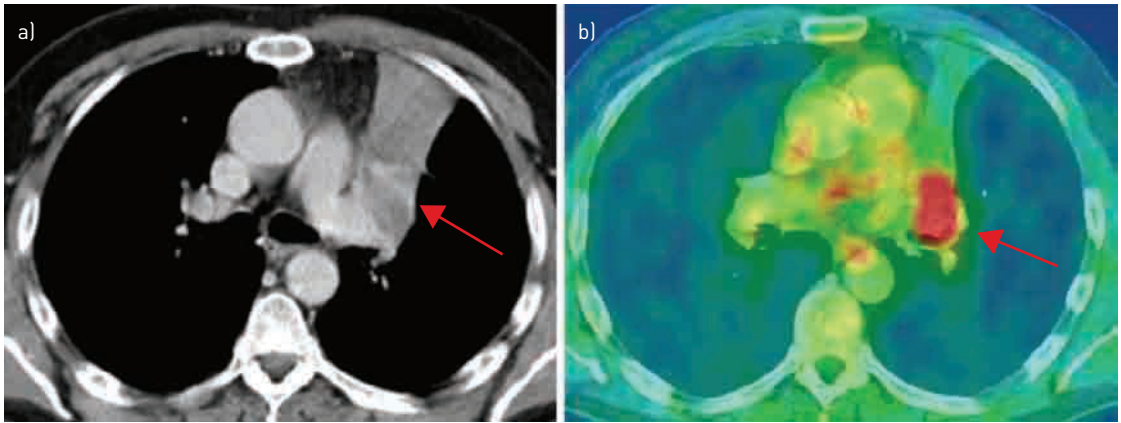


Figure 2 – a) Axial computed tomographic (CT) image showing a central tumour (arrow) in the left lung with a post-stenotic atelectasis (collapse) of the left upper lobe. b) The integrated positron emission tomography/CT image shows a hot spot (red) located on the central tumour (arrow), allowing discrimination between tumour and post-stenotic atelectasis. Reproduced from DE WEVER *et al.*, 2011.

enhancement (in suspected pulmonary embolism cases, for example). CT is also helpful for guiding needle aspiration of peripheral lung lesions. High-resolution CT (HRCT) has improved the diagnosis of diffuse interstitial lung disease considerably. Low-dose CT is used in follow-up and serial early lung cancer detection. CT can be used for virtual bronchoscopy or angiography, but this has not become routine. CT is applied in combination with positron emission tomography (PET) mainly for staging lung cancer and other malignancies, and in the differential diagnosis between benign and malignant lung lesions (figure 2). CT/HRCT has almost wholly replaced bronchography for the diagnosis of bronchiectasis.

Pulmonary and bronchial angiography

Pulmonary angiography and bronchial angiography (together with bronchial artery embolisation for the treatment of haemoptysis) are invasive techniques for imaging vessels and are only used if less invasive techniques (contrast CT/magnetic resonance imaging (MRI)) fail or need to be confirmed.

Fluoroscopy

Fluoroscopy (an X-ray technique by which respiratory movement is visualised directly) is used mainly for guidance of biopsy of peripheral lung lesions and for differential diagnosis of an elevated diaphragm.

Magnetic resonance imaging

MRI has the advantage that radiation is avoided. Its main indications are visualisation of the great vessels and the heart, but it is also useful with suspected tumour invasion of the mediastinum and the chest wall.

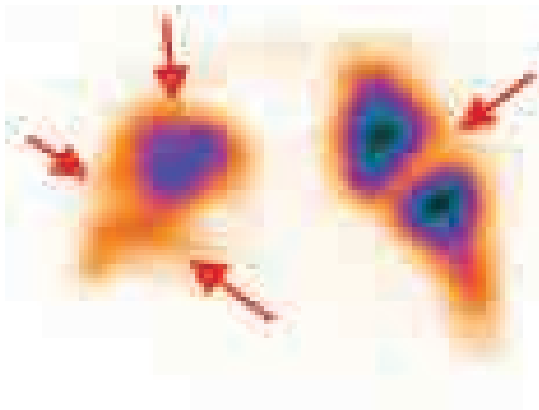


Figure 3 – Perfusion scintigram showing multiple areas with absent perfusion (arrows) in a patient with pulmonary emboli. Reproduced from BAJC, 2012.

Ultrasonography

Ultrasonography has become an important imaging technique. Its advantages are lack of radiation, low cost and mobility. It is mainly used in the investigation of pleural effusions (in which it also has a role in guiding thoracentesis) but also in pleural thickening, chest wall abnormalities, for the diagnosis of pneumothorax and for biopsies of lesions adjacent to the chest wall. A special application is endobronchial ultrasound (EBUS), which can be used for visualisation of mediastinal lymph nodes as well as pulmonary parenchymal lesions. Its most important use is the sampling of mediastinal lymph nodes in the setting of endoscopic lung cancer staging, where EBUS has largely replaced mediastinoscopy. Echocardiography allows noninvasive screening for pulmonary hypertension, although right heart catheterisation may be needed for the final diagnosis.

Nuclear medicine techniques

Nuclear medicine techniques include perfusion and ventilation scintigraphy, which are mainly indicated in the diagnosis of pulmonary embolism (figure 3) but also for regional lung function studies, *e.g.* for predicting post-operative lung function before lung surgery. Inhalation scintigraphy can be used to investigate mucociliary clearance.

Invasive biopsy techniques

Endoscopy and biopsy techniques are essential tools in many respiratory diseases when simpler clinical and laboratory methods of investigation have failed to yield a diagnosis. The results of biopsies are heavily dependent upon the quality of the pathological and microbiological examinations.

Bronchoscopy

The most important endoscopic method in respiratory medicine is bronchoscopy; for diagnostic purposes, this is almost exclusively performed with a flexible bronchoscope using video-assisted imaging, usually under local anaesthetic (figure 4). Bronchoscopy is associated with very few complications. The procedure not only allows inspection and sampling of the airways, but also facilitates transbronchial needle aspiration (TBNA)

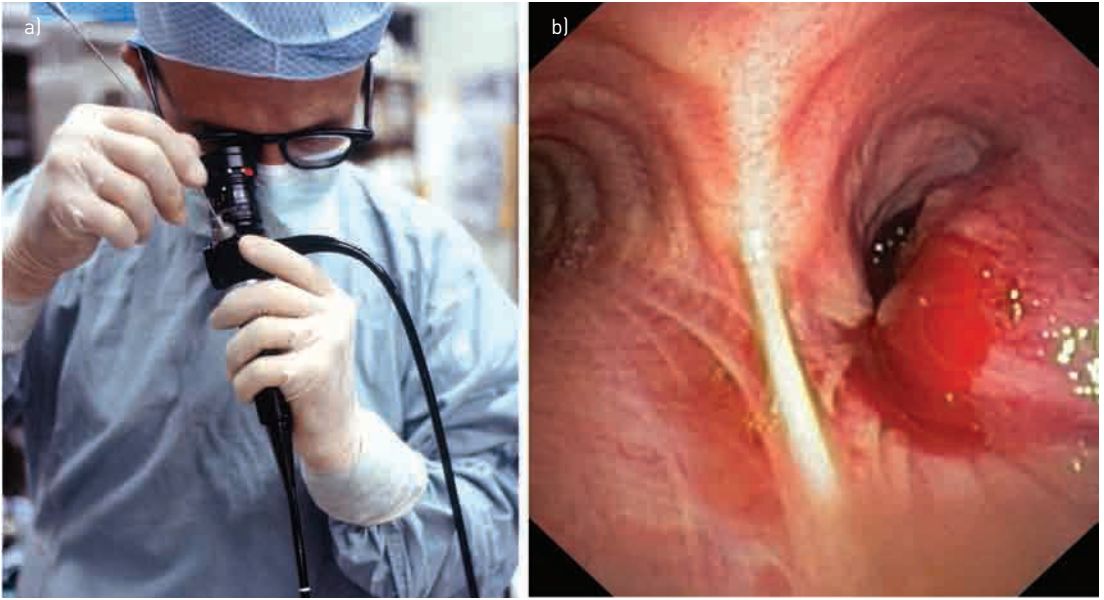


Figure 4 – a) Transbronchial needle aspiration during flexible bronchoscopy. b) Flexible bronchoscopy showing a tumour that is almost completely obstructing the right main bronchus, indicating inoperability due to the location of the tumour. Reproduced from HERTH, 2011.

from the lymph nodes, sampling material from peripheral lesions with special catheters and brushes, or transbronchial lung biopsy (TBLB) by forceps, often under guidance of EBUS or fluoroscopy. A more elaborate technique to guide the bronchoscopist to small lesions is electromagnetic navigation.

Bronchoalveolar lavage

Bronchoalveolar lavage (BAL) involves the instillation of saline via a bronchoscope in order to collect specimens for cytological or microbiological investigation. It is used mainly in interstitial lung diseases or lower respiratory tract infections, as material can easily be obtained from the periphery of the lung.

Autofluorescence and narrow-band imaging

Autofluorescence or narrowband imaging may be helpful in the detection of precancerous lesions and early cancers located in the bronchial tree.

Percutaneous needle biopsy

Percutaneous (or transthoracic) needle biopsy is mainly performed to investigate peripheral lung lesions when bronchoscopy is negative. It is performed with the guidance of either fluoroscopy or, preferably, CT. When lesions are adjacent to the chest wall, ultrasound guidance can also be used.

Thoracentesis and pleuroscopy (medical thoracoscopy)

Thoracentesis (pleural fluid aspiration or 'tap') is a frequently performed procedure in pleural effusions, preferably used under ultrasound guidance, at least when the effusion is small. Additional biopsy procedures, such as closed-needle biopsy of the pleura or pleuroscopy (medical thoracoscopy), may be necessary to confirm or exclude malignant or tuberculous causes of an effusion.

Surgical methods

Surgical investigative methods include mediastinoscopy and the minimally invasive technique of video-assisted thoracic surgery (VATS). Mediastinoscopy is used for biopsy of mediastinal lymph nodes (if TBNA is negative). VATS has almost completely replaced the use of open surgery for diagnostic purposes in intrathoracic lesions (including interstitial lung disease), in which the aetiology remains uncertain after performance of the above less invasive procedures.

Further reading



- Bajc M. Potential of hybrid V/P SPECT-low-dose CT in lung diagnostics. *Breathe* 2012; 9: 49–60.
- De Wever W, Coolen J, Verschakelen JA. Imaging techniques in lung cancer. *Breathe* 2011; 7: 338–346.
- Garbe B. Achieving quality spirometry in the office. *Breathe* 2010; 6: 211–219.
- Gibson GJ, Geddes DM, Costabel U, *et al.*, eds. *Respiratory Medicine*. 3rd Edn. Edinburgh, Saunders Elsevier Science, 2003.
- Herth FJF. Bronchoscopic techniques in diagnosis and staging of lung cancer. *Breathe* 2011; 7: 324–337.
- Loddenkemper R, Séverin T, Eiselé J-L, *et al.* HERMES: a European core syllabus in respiratory medicine. *Breathe* 2006; 3: 59–69.
- Mason RJ, Broaddus VC, Martin T, *et al.* eds. *Murray and Nadel's Textbook of Respiratory Medicine*. 5th Edn. Philadelphia, Saunders Elsevier, 2010.
- Palange P, Simonds AK, eds. *ERS Handbook of Respiratory Medicine*. 1st Edn. Sheffield, European Respiratory Society, 2010.