Radiological features of bronchiectasis

P.L. Perera* and N.J. Screaton #

Summary

Imaging plays a crucial role in the diagnosis and monitoring of bronchiectasis and the management of complications. Chest radiography is useful as an initial screening tool and during acute exacerbations, but has limited sensitivity and specificity. High-resolution computed tomography (HRCT) is the reference standard for diagnosis and quantification of bronchiectasis, providing detailed morphological information. Computed tomography (CT) is also valuable in diagnosing and managing complications. Routine surveillance using HRCT has been mooted, particularly in cystic fibrosis (CF), where advances in treatment have increased life expectancy considerably, but cumulative radiation dose remains a concern.

Pulmonary magnetic resonance imaging is an evolving technique that provides both structural and functional information. Its advantage is the lack of ionising radiation. Limitations include cost, availability and its inferior spatial resolution compared to CT. The technique requires further evaluation, but has potential benefits where serial follow-up imaging is being considered, such as in CF. Evaluation of mucociliary clearance using radionuclide scintigraphy may be of value, particularly in drug development.

Keywords: Bronchiectasis, cystic fibrosis, diagnostic imaging, magnetic resonance imaging, mucociliary clearance, spiral computed tomography

Bronchiectasis is characterised by irreversible dilation of bronchi, which may be focal or diffuse, and usually occurs with associated inflammation. Its pathogenesis is complex and often multifactorial, with bronchial wall inflammation, bronchial wall weakness and infection often occurring in parallel and with numerous aetiological factors. Since it was first described by LAENNEC [1] in 1819, there have been considerable advances in the understanding, diagnosis and treatment of bronchiectasis. Imaging now forms the cornerstone of diagnosis of bronchiectasis and its complications and plays an increasing role in disease monitoring and therapeutic planning. The present review focuses on imaging features in bronchiectasis and their role in diagnosis and monitoring of disease. Several imaging modalities are available, with varying strengths and
limitations, which are outlined below. The choice of diagnostic/monitoring strategy shows some variation depending on access to each modality and interpretive expertise. Image-guided intervention, such as percutaneous pleural aspiration/drainage and angiography with embolisation play important roles in treating complications, but are beyond the scope of the present review.

**Chest radiography**

Chest radiography (CXR) is usually the initial study performed in both suspected bronchiectasis and the evaluation of nonspecific respiratory symptoms, such as dyspnoea and haemoptysis, when bronchiectasis may be identified incidentally. Signs on CXR include the identification of parallel linear densities, tram-track opacities, or ring shadows reflecting thickened and abnormally dilated bronchial walls. These bronchial abnormalities form a spectrum from subtle or barely perceptible 5-mm ring shadows to obvious cysts. Tubular branching opacities conforming to the expected bronchial branching pattern may result from fluid or mucous filling of bronchi. Peribronchial fibrosis results in a loss of definition of vessel walls (fig. 1) [2–5].

Signs of complications/exacerbations, such as patchy densities due to mucoid impaction and consolidation, volume loss secondary to bronchial mucoid obstruction or chronic cicatrisation, are also seen. In the more diffuse forms of bronchiectasis, such as cystic fibrosis (CF), generalised hyperinflation and oligaemia are often present, consistent with severe small airways obstruction. The radiograph may raise the initial suspicion of bronchiectasis, triggering more definitive imaging. However, its projectional nature and limited contrast resolution lead to limited sensitivity and specificity, particularly in mild disease. CXR also plays a role in the follow-up of bronchiectasis and management of exacerbations, although, again, the relative insensitivity to change is highlighted by proponents of computed tomography (CT) and magnetic resonance (MR) imaging (MRI) [2–5].

The reported accuracy of CXR has changed over the years as the management emphasis has shifted from being reactive to complications to one of early detection and proactive management, and as the diagnostic reference standard has shifted from bronchography to CT. In 1955, GUDJBERG [6] reported only 7.1% of 114 bronchiectatic patients having a normal CXR, perhaps reflecting the more florid nature of the condition during this period. In 1987, CURRIE et al. [7] reported an overall sensitivity of 47%, and only 13% on a lobar basis, in 19 patients with bronchographically proven bronchiectasis. The same study confirmed significant interobserver variation in CXR interpretation, with two experienced readers disagreeing on the diagnosis of bronchiectasis in 22% of cases [7].

In comparison to CXR, CT is both more sensitive and provides more specific information. BHALLA et al. [8] showed that, out of a total of 162 bronchopulmonary segments reviewed, bronchiectasis was detected in 124 on high-resolution CT (HRCT) and only 71 on CXR.

Radiographic scoring systems, such as those of CHRISPIN and NORMAN [9] and BRASFIELD et al. [10], have been developed and subsequently modified for patients with CF. These can be useful clinically, but are more commonly used for comparison in research. CLEVELAND et al. [11] showed that a score based on the scoring system of BRASFIELD et al. [10] could be used to assess the longitudinal progression of lung disease in CF, and was at least as effective as spirometry in this regard.

Although CXR has limitations in specificity in diagnosing bronchiectasis and in detecting early or subtle changes, it is useful for assessing more florid cases of bronchiectasis, in CF and in follow-up of bronchiectatic patients.

**Computed tomography**

The CT signs of bronchiectasis were first described by NAIDICH et al. [12] in 1982. Although initial studies using 8–10-mm slice thickness showed low sensitivity [13–15], the advent of HRCT led to markedly improved sensitivity, resulting in HRCT replacing bronchography as the diagnostic reference standard. GRENIER et al. [16] showed that HRCT with 1.5-mm collimation at 10-mm
intervals was accurate in the recognition of bronchiectasis using bronchography as the gold standard in 36 patients.

Multidetector CT (MDCT) with volumetric acquisition further increases the sensitivity in detection of subtle nontapering airways. Dodd et al. [17] compared contiguous 1-mm MDCT with 1-mm incremental HRCT with 10-mm interspaces in 61 bronchiectatic patients and 19 normal controls. Using MDCT as the gold standard, the sensitivity, specificity and positive and negative predictive values of incremental HRCT in detecting bronchiectasis were 71, 93, 88 and 81%, respectively. Interobserver agreement for the presence, extent and severity of bronchiectasis was also better for MDCT (kappa 0.64, 0.5 and 0.48, respectively) than for incremental HRCT (kappa 0.65, 0.46 and 0.25, respectively).

Optimal HRCT technique is important for maximising diagnostic accuracy. Importantly, thin slices of 1–2 mm and a high-resolution lung reconstruction algorithm are used to optimise spatial resolution. Incremental imaging with 10-mm slice interspace reduces radiation dose, but helical MDCT permits volumetric acquisition in a single breath-hold, which is often the preferred technique. Electronic images should be viewed in stack/cine mode using the appropriate window settings (centred -400–-950 HU; width 1,000–1,600 HU). Difficulties in diagnosing bronchiectasis can arise from cardiorespiratory motion artefact, use of inappropriate window widths and levels, and the relatively thick-walled appearance of bronchial walls on expiratory scans. Tractional airway dilation associated with pulmonary fibrosis has a characteristic corkscrew appearance and should be differentiated from pathological bronchiectasis.

CT signs of bronchiectasis

Bronchial dilation, the cardinal sign of bronchiectasis, is characterised on HRCT by a bronchoarterial ratio (BAR) of >1, lack of bronchial tapering, and visibility of airways within 1 cm of the pleural surface or abutting the mediastinal pleural surface [2, 12, 16, 18, 19].
The different morphological types of bronchiectasis corresponding to the bronchographic classification of Reid [20] show differing radiological features [16, 21], but this is of little relevance in terms of aetiology and rather reflects varying severity of the disease. Although, in cylindrical bronchiectasis, there is uniform dilation of airways with nontapering walls, in varicose bronchiectasis, dilated bronchi have a beaded appearance and, in cystic bronchiectasis, grosser bronchial dilation gives the appearance of cysts (fig. 2).

The BAR refers to the ratio of the internal bronchial diameter to the diameter of the accompanying pulmonary artery at an equivalent branching level. A BAR of >1 is considered abnormal [14, 15, 19] and is otherwise known as the signet-ring sign (fig. 3).

The accuracy of the BAR can be limited by a number of factors, including physiological variation and orientation of the bronchovascular bundle with respect to the imaging plane [16, 22, 23]. Comparison is best performed on perpendicularly orientated airways. When oblique to the acquisition plane, airways and vessels appear ovoid and their short axis should be compared.

Physiological influence on BAR was highlighted by Lynch et al. [23], who showed that 59% of 27 normal volunteers living in Colorado, USA (1,600 m above sea level) had at least one bronchus that had an internal diameter larger than its accompanying artery. Kim et al. [18] confirmed this environmental influence on BAR by demonstrating that residents living at 1,600 m exhibited significantly higher BARs than those living at sea level (0.76 and 0.62, respectively; p<0.001). Physiological variation can also occur due to regional hypoxia, and so secondary vasoconstriction causing apparent bronchial dilation must be recognised in order to prevent a spurious diagnosis of bronchiectasis. Conversely, if there is arterial dilation (e.g. due to pulmonary arterial hypertension), bronchiectasis could be missed. A practical problem in assessing BAR is the need to identify the accompanying artery, which may be difficult in the presence of other lung pathology, such as consolidation. In the setting of consolidation, the presence of bronchial dilation may be a reversible phenomenon and so caution should be observed when interpreting CT data during an acute illness.

Although objective measurement may be performed, visual inspection is the usual method of assessing bronchial dilation. Diederich et al. [24] showed this to have good interobserver agreement for detection (kappa 0.78) and severity assessment (kappa 0.68).

Lack of bronchial tapering or tram-track appearance of the parallel bronchial walls is a sensitive feature of bronchiectasis often identified in more horizontally orientated airways in the mid-zones. Kang et al. [25] showed that lack of tapering on HRCT was more sensitive than bronchial dilation in bronchiectasis (79 and 60%, respectively) using pathology as the reference standard. However, the sign can be difficult to interpret in nonvolumetric CT studies. Kim et al. [18] demonstrated lack of tapering on HRCT in 95% of patients with bronchiectasis, but also in 10% of normal subjects. It has been suggested that bronchial diameter should remain unchanged for at least 2 cm distal to a branching point for this sign to be robust (fig. 4) [26].
Visibility of peripheral airways is another important direct sign of bronchiectasis [17]. Current HRCT techniques permit visualisation of airways of up to 2 mm in diameter and walls of around 0.2 mm in thickness. KIM et al. [18] showed that normal bronchi are not visualised within 1 cm of the costal pleura, but may be seen within 1 cm of the mediastinal pleura. Visible bronchi within 1 cm of the costal pleura or abutting the mediastinal surface were seen in 81 and 53% of HRCT images of known bronchiectatic patients (fig. 4).

Ancillary signs commonly identified in bronchiectatic patients include bronchial wall thickening, mucoid impaction and air-trapping. Minor volume loss can be seen in the early stages of bronchiectasis. Larger areas of collapse secondary to mucous plugging may be seen in more advanced disease. Patchy consolidation is sometimes seen reflecting superimposed infection.

Bronchial wall thickening is often seen in the presence of bronchiectasis [25], but is a variable nondiagnostic feature. It may result from reversible airway wall inflammation [27] or smooth muscle hypertrophy and fibroblastic proliferation. Minor bronchial wall thickening has, however, also been described in normal individuals, asthmatics, asymptomatic smokers and during lower respiratory tract infections [23, 28].

Identification of bronchial wall thickening on HRCT is often made subjectively and is associated with significant interobserver variation, with no universally agreed definition. REMY-JARDIN and REMY [28] defined a thickened bronchus as being twice as thick as a normal bronchus; however, this definition is difficult in diffuse disease DIEDERICH et al. [24] defined a thick-walled bronchus by an internal diameter of <80% of its external diameter and showed good interobserver agreement (kappa 0.66). However, this can lead to overdiagnosis of thickening in the presence of bronchoconstriction and underestimation with marked bronchodilation. An alternative approach, used by BHALLA et al. [8] in CF and subsequently modified by REIFF et al. [29], is to compare bronchial wall thickness to the diameter of the adjacent artery. As with assessment of BAR, peribronchial fibrosis and consolidation pose practical difficulties in identifying accompanying vessels (fig. 5).

Mucous plugging of dilated bronchi is readily identified, causing either complete or partial luminal filling (fig. 5). Plugging of the smaller peripheral airways and peribronchiolar inflammation are characterised by a tree-in-bud appearance, with V- and Y-shaped branching nodular opacities [30]. Mucous plugging was scored in terms of number and generation of involved bronchopulmonary segments using the scoring system of BHALLA et al. [8], and may be reversible.

Air-trapping results either from mucous plugging and abnormal bronchial compliance [31] or inflammation/ fibrosis of the small airways [2]. On HRCT, air-trapping is characterised by patchy lobular areas of low attenuation with regional vasoconstriction, which causes a mosaic attenuation pattern, accentuated on expiratory images, although inspiratory images are usually characteristic (fig. 6). Air-trapping and bronchiectasis coexist in the same lobe in approximately half of cases [25]. Whether it is the bronchiectasis and recurrent infections driving obliterative bronchiolitis (OB) or primary small airways disease that precedes the
onset of bronchiectasis is debated, and may vary [31]. The latter is supported both by the observation that, in patients with CT-proven bronchiectasis, expiratory HRCT identifies air-trapping in 17% of lobes with no bronchiectatic features and that, in patients with rheumatoid arthritis (RA)-associated OB, the onset of symptoms and obstructive function may predate the onset of bronchiectasis by several years [32].

**Imaging and aetiology of bronchiectasis**

There are many aetiologies associated with bronchiectasis, but a specific underlying cause is found in <40% of patients [33]. In some cases, the distribution and pattern of bronchiectasis on HRCT may suggest the aetiology. Allergic bronchopulmonary aspergillosis (ABPA) typically demonstrates an upper zone and central predominance [34–37], hypogammaglobulinaemia may be associated with bronchiectasis with disproportionate bronchial wall thickening, middle lobe predominance is common in immotile cilia syndrome [38] and idiopathic bronchiectasis often has a lower lobe distribution [39].

However, in a large study comparing HRCT features in bronchiectasis of defined aetiology with idiopathic bronchiectasis, REIFF et al. [29] concluded that, although some HRCT features were more common in some aetiological groups, the differences were not sufficient to be diagnostic. LEE et al. [40] reinforced this observation in a study of 108 bronchiectatic patients in whom the correct cause was identified on CT in only 45% of cases. A confident diagnosis was asserted in a minority (9%) and was correct in only 35%. Interobserver agreement in likely aetiology was also poor (kappa 0.2) [40]. However, more recently, CARTIER et al. [41] obtained accurate diagnoses on the basis of HRCT in 61% of 82 patients with bronchiectasis of known cause, with moderately good agreement (kappa 0.53). Confident and accurate diagnosis was made in 44% of patients (kappa 0.53). Accuracy was highest in CF (68%), previous tuberculosis (67%) and ABPA (56%). Part of the reason for the higher number of accurate diagnoses was attributed to the exclusion of patients in whom the aetiology of bronchiectasis was not known. They concluded that the combination of radiological pattern and clinical scenario would have improved the accuracy of the evaluation.

HRCT is important in the assessment of mycobacterial infection. This is particularly true of nontuberculous mycobacteria (NTM), where the diagnosis is often first suggested on HRCT. CT signs of NTM include bronchiectasis, nodules, tree-in-bud opacity, patchy consolidation and cavities, often affecting the upper lobes and superior segments of lower lobes in the classic subtype and middle lobe/lingula in the nonclassic subtype [42]. The presence of this combination of features with a middle lobe and lingual predominance, especially in the setting of elderly females with no underlying malignancy or immunocompromise, is particularly suggestive of nonclassic NTM [43, 44]. Bronchiectasis is more common in NTM infection, being seen in up to 94% of patients with *Mycobacterium avium* complex and 27% of patients with *M. tuberculosis* [45].

Bronchiectasis in CF usually has a bilateral, proximal, parahilar and upper lobe predominance. Other findings include bronchial wall thickening, peribronchial interstitial thickening, mucous plugging, tree-in-bud opacification, superadded consolidation and mosaic attenuation. SHAH et al. [27] assessed the CT changes in 19 symptomatic adult CF patients before and after 2 weeks of therapy and identified air–fluid levels in bronchiectatic airways, mucous plugging, centrilobular nodules and peribronchial thickening as potentially reversible signs.

Bronchiectasis with a central or proximal predominance is the characteristic finding in ABPA (fig. 7a). REIFF et al. [29] showed that the prevalence of central bronchiectasis was higher in ABPA (11 out of 30) than in idiopathic bronchiectasis (26 out of 179) (p<0.005). However, the sensitivity of the observation of central bronchiectasis in diagnosing ABPA was only 37%. PANCHAL et al. [46]
demonstrated central bronchiectasis in 85% of lobes and 52% of lung segments in a series of 23 patients with ABPA. Other common findings in ABPA include mucous plugging, high-attenuation mucus, tree-in-bud opacities, atelectasis, peripheral consolidation or ground-glass opacification, mosaic perfusion and air-trapping. The bronchiectasis is often cystic or varicose. Ward et al. [47] assessed CT images from 44 asthmatic patients with ABPA and 38 without and found much higher levels of bronchiectasis, centrilobular nodules and mucous impaction in ABPA. They concluded that randomly distributed predominantly central moderate-to-severe bronchiectasis affecting three or more lobes, bronchial wall thickening and centrilobular nodules in asthmatics is highly suggestive of ABPA (fig. 7b).

High-attenuation mucous plugs are reported to occur in 18–28% of patients with ABPA, and, if observed, are thought to be characteristic [48–50]. In a study of 155 patients with ABPA, Agarwal et al. [48] found this sign in 29 patients, and that it correlated with greater severity and greater likelihood of relapse.

In summary, there are some recognised clinical conditions in which assessment of bronchiectasis forms an important part of management. CT images in bronchiectatic patients should be examined for features suggesting ABPA, CF, immotile cilia, opportunistic mycobacteria and tracheobronchomegaly, but these observation need to be correlated with clinical and laboratory findings.

**CT scoring of bronchiectasis**

Although the extent, severity and distribution of bronchiectasis may be evaluated subjectively, more-robust objective scoring systems have been developed particularly for use in the research arena. With the development of novel software tools, it is now possible to objectively quantify parameters, such as airway wall area and volume, in a semi-automatic manner. Both subjective and objective quantification permit correlations between structure and function to be evaluated.

CT scoring systems are based on collective scores for the extent and distribution of a range of morphological abnormalities, including bronchial dilation, bronchial thickening, abscesses, mucous plugging, emphysema, collapse and consolidation.

The HRCT score of Bhalla et al. [8] was devised to evaluate the severity of CF in an objective manner. Severity of bronchial dilation and thickening were defined relative to the adjacent pulmonary artery, and other parameters were scored according to the number of bronchopulmonary segments involved, as shown in table 1. This scoring system has been modified many times, and has also been adapted for use in MRI assessment of CF. Modifications have included incorporation of additional findings, such as air-trapping/mosaic attenuation, ground-glass opacification, acinar nodules and septal thickening, with some scores being per segment and others based on lobar scoring. Each scoring system attempts to produce both a total score, by combining features, and specific morphological scores. These have been demonstrated to be more sensitive to disease and show better correlation with both clinical features and lung function than the CXR-based scoring systems. Oikonomou et al. [51]
suggested a simplified scoring system evaluating severity of bronchiectasis, bronchial wall thickening and atelectasis consolidation. They found strong correlation between the simplified scores and the complete scores.

Shah et al. [27] used a modified Bhalla score in bronchiectatic patients undergoing HRCT at baseline and 2 weeks after exacerbation in order to identify reversible findings, and showed that air–fluid levels, centrilobular nodules, mucous plugging and peribronchial thickening improved following treatment in 100, 36, 33 and 11% of cases, respectively.

De Jong et al. [52] compared the original scoring system of Bhalla et al. [8] and four modified Bhalla systems [53–56]. Three observers reviewed thin-slice CT images of 25 children with CF using the various scoring systems. Interobserver variability was analysed using kappa coefficients and found to be generally good (kappa >0.76; p<0.05). However, inter- and intra-observer agreement was less for mild disease, as well as for parameters such as mosaic perfusion, acinar nodules and airspace disease. All five scoring systems correlated strongly with forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), forced expiratory flow between 25 and 75% of vital capacity (FEF25–75), FEV1/FVC ratio and each other.

Quantitative computerised evaluation of the airways presents a number of challenges, including obtaining a plane perpendicular to the airway, exclusion of the adjacent artery, determining the borders of the bronchus, artefacts and partial volume averaging. Three different methods have been used to obtain airway measurements, full width at half maximum, model fitting approaches and boundary fitting approaches [19]. A detailed description of these techniques is beyond the scope of the present chapter.

Goris et al. [57] looked at automated evaluation of the extent of air-trapping in 25 patients with mild CF compared to 10 controls; six anatomically matched CT slices were obtained during

**Table 1. Summary of computed tomography scoring system**

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity of bronchiectasis</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>Mild (luminal diameter slightly greater than that of adjacent blood vessel)</td>
</tr>
<tr>
<td>1</td>
<td>Moderate (luminal diameter 2–3 times that of adjacent blood vessel)</td>
</tr>
<tr>
<td>2</td>
<td>Severe (luminal diameter &gt;3 times that of adjacent blood vessel)</td>
</tr>
<tr>
<td><strong>Peribronchial thickening</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>Mild (wall thickness equal to diameter of adjacent vessel)</td>
</tr>
<tr>
<td>1</td>
<td>Moderate (wall thickness greater than and up to twice the diameter of adjacent vessel)</td>
</tr>
<tr>
<td>2</td>
<td>Severe (wall thickness &gt;2 times the diameter of adjacent vessel)</td>
</tr>
<tr>
<td><strong>Extent of bronchiectasis</strong></td>
<td></td>
</tr>
<tr>
<td>BP segments n 1–5</td>
<td>Present</td>
</tr>
<tr>
<td>BP segments n 1–5</td>
<td>Present</td>
</tr>
<tr>
<td>BP segments n 1–5</td>
<td>Present</td>
</tr>
<tr>
<td>BP segments n 1–5</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Extent of mucous plugging</strong></td>
<td></td>
</tr>
<tr>
<td>BP segments n 1–5</td>
<td>Present</td>
</tr>
<tr>
<td>BP segments n 1–5</td>
<td>Present</td>
</tr>
<tr>
<td>BP segments n 1–5</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Sacculations or abscesses</strong></td>
<td></td>
</tr>
<tr>
<td>BP segments n 1–5</td>
<td>Present</td>
</tr>
<tr>
<td>BP segments n 1–5</td>
<td>Present</td>
</tr>
<tr>
<td>BP segments n 1–5</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Bronchial divisions involved</strong></td>
<td></td>
</tr>
<tr>
<td>BP: bronchopulmonary</td>
<td></td>
</tr>
<tr>
<td><strong>Emphysema</strong></td>
<td></td>
</tr>
<tr>
<td>BP segments n 1–5</td>
<td>Present</td>
</tr>
<tr>
<td>Bullae</td>
<td>Unilateral</td>
</tr>
<tr>
<td>Not &gt;4</td>
<td>Bilateral</td>
</tr>
<tr>
<td><strong>Collapse/consolidation</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>Subsegmental</td>
</tr>
<tr>
<td>1–5</td>
<td>Segmental/lobar</td>
</tr>
</tbody>
</table>

BP: bronchopulmonary. Reproduced from [8] with permission from the publisher.
Computerised lung segmentation was performed and automated software used to quantify air-trapping, using analysis of a histogram of the distribution of densities in the lung, and assessing contiguous low-attenuation voxel regions. In mild CF, air-trapping did not correlate with global pulmonary function test (PFT) results, except for the ratio of residual volume (RV) to total lung capacity (TLC); however, the size of the air-trapping defects was the best discriminator between patients and control subjects (p<0.005).

Kiraly et al. [58] looked at fully automated methods of obtaining three-dimensional (3D) images and quantification of airway abnormalities. Working from thin-slice image acquisition and using computerised segmentation techniques, they obtained 3D images of the airways with colour-coded maps showing BAR, wall thickness and mucous plugging. These have, however, not been fully clinically validated.

Although these objective tools are interesting, further studies are required to evaluate the various computerised imaging parameters and their relation to functional and clinical findings in bronchiectasis. A note of caution was raised by Matsuoka et al. [59], who used semi-automatic image processing to assess the airways of 52 asymptomatic patients with no cardiopulmonary disease. They found that luminal area and wall area increased in 10 and 29% of subjects, respectively, suggesting caution in over-reliance on changes in airway calibre in disease monitoring.

Structure–function relationships

Relationships between HRCT data and functional and clinical characteristics have been widely explored. Wong-You-Cheong et al. [60] showed a clear negative correlation between FEV1 and extent of bronchiectasis on HRCT (p<0.002; r= -0.43). Smith et al. [61] showed correlation between extent of bronchiectasis on HRCT and both dyspnoea (p<0.01; r=0.38) and FEV1 (p<0.01; r= -0.43). More recently, De Jong et al. [52] showed strong correlations between five scoring systems [8, 53–56] and FEV1 (r= -0.69– -0.73), FEF25–75 (r= -0.76– -0.82) and FEV1/ FVC ratio (r= -0.72– -0.78). Correlation with FVC was moderate (r= -0.54– -0.58).

Authors have investigated which morphological abnormalities are most strongly associated with a functional deficit. Lynch et al. [62], in a study of 261 bronchiectatic patients, found significant correlation between severity of bronchiectasis, FEV1 (r= -0.362) and FVC (r= -0.362), and between bronchial wall thickening and FEV1 (r= -0.367) and FVC (r= -0.239). Cystic bronchiectasis was found to show worse PFT results than cylindrical or varicose disease.

In a study of 100 patients with bronchiectasis, Roberts et al. [63] found good correlation between FEV1 and bronchial wall thickening (r= -0.51; p=0.00005) and extent of decreased attenuation on expiratory HRCT (r= -0.55, p=0.00005) on univariate analysis. These were the only factors that independently correlated with degree of airflow limitation on multivariate analysis. In this study, obstructive lung function was not strongly associated with severity of bronchiectasis, bronchodilation, or retained sections in bronchiectasis (r= -0.42, -0.35 and -0.19, respectively, on univariate analysis). Bronchial dilation as an independent factor was positively associated with airflow obstruction on regression analysis (r²=0.42). The authors concluded that airflow limitation in bronchiectasis occurred mainly due to inflammatory or obstructive/constrictive bronchiolitis. They also suggested that areas of low attenuation attributed to emphysema in bronchiectatic patients in previous studies (e.g. [64]) should be interpreted with caution, suggesting that the emphysema demonstrated was often due to air-trapping related to intrinsic small airways disease rather than emphysema, as evidenced by preserved gas transfer in the both of these studies.

HRCT scoring can also be correlated with clinical parameters. In a study of 61 CF children, baseline and follow-up PFT and HRCT scores were compared to the number of respiratory exacerbations over 2 years. Only the HRCT score (r=0.91; p=0.001) and bronchiectatic score (r=0.083; p=0.01) correlated significantly with exacerbation frequency. All HRCT parameters
progressed over this time period except for bronchial wall thickening and mucous plugging, suggesting that these are reversible features [65]. OOI et al. [66] studied 60 patients with stable bronchiectasis with HRCT. They showed good correlation between the extents of bronchiectasis, bronchial wall thickening and mosaic attenuation and FEV1 (r= -0.43—-0.60), FVC (r= -0.36—-0.46), FEF25–50 (r= -0.38—-0.57) and FEV1/FVC (r= -0.31—-0.49). Regression analysis showed that extent of bronchiectasis and wall thickening were the most significant determinants of airflow obstruction, correlating with all PFT parameters. This study also demonstrated associations between bronchial wall thickening and clinical factors, such as exacerbation frequency and 24-hour sputum production (r= -0.32 and -0.30). Alzeer [67] found that the HRCT score correlated well with FEV1 (r= -0.51), as well as with systolic pulmonary artery pressure (Ppa,sys) (r=0.23), in a study of 94 bronchiectatic patients.

Studies on the utility of HRCT in the follow-up of non-CF bronchiectatic patients have been limited. In a study of 48 patients, Sheehan et al. [68] compared serial CT studies with PFTs, showing correlation of changes in PFT results with air-trapping due to mucous plugging. Greater severity of mucous plugging, bronchiectasis and bronchial wall thickening were predictive of decreased FEV1. In a study evaluating morphological features in bronchiectasis at baseline and 2 weeks after exacerbation, Shah et al. [27] showed that changes in HRCT score during exacerbation of bronchiectasis also correlated with improvement in FEV1/FVC (r=0.39; p=0.049). Severity of bronchiectasis was the component most strongly associated with PFT results (r=0.4 for FEV1 and r=0.5 for FVC), whereas tree in bud and mucous plugging were not strongly correlated.

The validity of the use of PFTs as the gold standard in evaluating HRCT has been questioned by several authors. Brody et al. [69] and Helbich et al. [53] have shown that early HRCT changes, including mosaic attenuation and bronchial dilation, can be seen early in disease in the presence of normal PFT results. Long et al. [70] showed HRCT changes, including wall thickening and bronchial dilation in CF infants with a mean age of 2 years, further emphasising the sensitivity of HRCT.

Regular low-dose HRCT for the surveillance of CF has been adopted by several centres since the late 1990s [71]. This was initially in the form of 1-mm slice incremental HRCT (with 10-mm interspaces), but, more recently, of full-lung volumetric HRCT. CT is performed as early as an age of 2 years, when it is performed as controlled-ventilation CT (CVCT), requiring sedation or general anaesthesia. The rationale for using this imaging-intensive approach is that PFT results may lag behind structural CT changes, difficulty in reliably performing PFTs in young children and the ability of imaging to follow relevant objective structural markers, such as bronchiectasis, bronchial wall thickening, air-trapping and mucous plugging. Furthermore, in the modern era, improved therapy has slowed the annual decline in PFT results such that individual variability and changes due to other factors, such as technique, puberty and infections, have made PFTs even less reliable for disease monitoring. However, the benefit has to be viewed in the setting of radiation risk. De Jong et al. [72] used a computational model to estimate mortality effects of regular CTs. The mean radiation dose for the published CT protocol was 1 mSv. Survival reduction associated with annual scans from the age of 2 years until death for CF patients with a median survival of 26 and 50 years, were approximately 1 month and 2 years, respectively. Cumulative cancer mortality was approximately 2 and 13% at age 40 and 65 years, respectively. Biannual CTs exhibit half the risk. This highlights the increasing reduction in survival with increasing age, an important point given the increasing life expectancy of CF patients.

De Jong et al. [73] studied 48 young patients with CF using serial low-dose HRCT and PFTs 2 years apart. In all children, there was progressive structural HRCT change with deterioration in HRCT scores by 2.2–3.5% overall, but particularly with peripheral extension of bronchiectasis and mucous plugging, despite stable (or, in some cases, improved) lung function. This may reflect poor PFT technique in young CF children, the use of predicted FEV1 (with reference to a global population) and/or the greater sensitivity of HRCT for detection of early and regional changes.
JUDGE et al. [74] assessed serial HRCT performed 18 months apart in 39 consecutive CF patients and found that the modified HRCT score declined faster (2.7% per year; p<0.001) than did FEV1 (2.3% per year). Six patients demonstrated worsening HRCT score with no change in PFT result. DE JONG et al. [75], in a study of 119 children and adults with CF, showed that PFT results, component and CT scores deteriorated over 2 years. The CT score (and its components) and PFT results showed similar rates of deterioration in adults and children (p>0.09). Peripheral bronchiectasis worsened by 1.7% per year in children (p<0.0001) and by 1.5% per year in adults (p<0.0001).

In view of the potential for discordance between morphology and function and the complementary nature of these variables, authors have attempted to create more-robust clinically useful composite scoring systems combining PFT results and HRCT findings [76].

Studies on assessment following therapy have been limited. ROBINSON et al. [76] used a composite scoring system using many of the HRCT parameters described above and combining them with PFT measures of obstructive function (FEV1 and FEF25–75). They showed the composite measurement to be more sensitive for assessing response to treatment in 25 CF children who were randomised to a treatment arm and a nebulised saline arm; FEF25–50 showed 13% improvement, global HRCT 5% and composite score 30%. Small studies have shown some HRCT features to be useful in post-treatment evaluation. NASR et al. [77] showed a significant improvement in total HRCT score following recombinant human (rh) deoxyribonuclease (DNAse) therapy compared to placebo. GORIS et al. [57] compared 25 CF patients with 10 age-matched controls using PFTs and automated quantitative assessment of lung density. No significant difference was seen in PFT results, but significant differences in air-trapping were seen, with the size of defects being the best discriminator. There was a significant decrease in mean HRCT score from 25 to 22 (p=0.014), with improvement in peribronchial thickening (p=0.007), mucous plugging (p=0.002) and overall appearance (p=0.025).

There have been some differences in the degree of correlation between PFT results and HRCT findings of bronchiectasis in the various studies, which could be attributed to several causes, including the scoring system used, radiological interpretation, parameters assessed, population studied, reliability of PFTs and data analysis (multivariate versus univariate). However, the link between measures of obstructive lung function (FEV1 and FEF25–50) and bronchial wall thickness/total HRCT score has been consistently shown.

**Role of HRCT in bronchiectasis**

CT is invaluable in the diagnosis of bronchiectasis, but also plays an important role in the evaluation of complications and assessment and monitoring of disease severity. HRCT provides good clinical correlation, and the use of scoring systems holds promise for monitoring of bronchiectasis. The more robust CT scoring systems have been formulated in CF patients. HRCT is sometimes of value in identifying the aetiology of bronchiectasis. Advantages of HRCT over PFTs include its ability to identify focal changes as well as provide a global score, in addition to assessing multiple parameters, some of which are reversible and others irreversible (fig. 8).

Current British Thoracic Society guidelines recommend HRCT at diagnosis and during exacerbations, but not for routine follow-up. An exception is in bronchiectasis secondary to humoral immunodeficiency, where follow-up HRCT may be beneficial [78].

HRCT is now widely regarded as part of the standard clinical evaluation of patients with CF. The ability to quantify extent and severity of disease and to serve as a useful outcome marker, and the potential for assessing treatment response, make this a particularly valuable investigation. However, although HRCT provides valuable information on initial assessment, the role and periodicity of serial imaging in CF remains controversial in view of increasing life expectancy and cumulative radiation exposure. Some authors suggest that HRCT should form part of the routine monitoring of CF, but with due consideration to the excess radiation [71]. With appropriate
scanning technique, it is estimated that a chest CT every other year from birth to age 30 years would involve an effective dose of 15 mSv compared to the mean background radiation dose over this period of 90 mSv [79].

Thus HRCT forms an important part of the investigation and diagnosis of bronchiectasis and exacerbations. It is particularly useful in CF, where it has been shown to be a good marker of outcome and has demonstrated the ability to pick up subtle and early changes with greater sensitivity than PFTs.

**Magnetic resonance imaging**

Interest in the use of MRI for lung imaging arose in the mid-1980s. The inherent difficulties in pulmonary MRI are well documented. Lungs have an intrinsically low proton density, which results in poor signal generation. This low signal is further degraded by susceptibility artefact resulting from the innumerable air–tissue interfaces and cardiac and respiratory motion. However, the advent of parallel imaging and new rapid imaging sequences have permitted marked improvement in temporal and spatial resolution. Although spatial resolution using conventional proton MRI is less than that using CT, MRI offers significant morphological information and has advantages in enabling improved tissue characterisation and providing functional imaging, including vascular flow and respiratory mechanics. The use of novel imaging techniques, such as oxygen-enhanced MRI and hyperpolarised helium-3 MRI, potentially permits derivation of further functional parameters, including regional ventilation, regional oxygen concentration and evaluation of lung microstructure using the apparent diffusion coefficient (ADC).

Although application of this technique currently lies largely in the research arena, a significant advantage of MRI is the lack of radiation, which is particularly important in patients who require recurrent imaging and the younger population group. This is pertinent when considering the potential cumulative lifetime radiation dose from annual/biannual low-dose CT examination in the CF population that are currently advocated by some groups [71], especially in view of the rapid improvement in life expectancy in this patient group, which is projected to continue. Thus it is unsurprising that much of the work on thoracic MRI imaging has been focused on patients with CF.

**Conventional proton MRI features**

Owing to the limited spatial resolution of MRI, assessment of bronchial wall thickness and bronchiectasis are dependent upon bronchial level, wall thickness and wall signal. Third-generation bronchi and beyond are poorly visualised on MRI, except in pathological states, when the wall and luminal signal are raised due to wall thickening, inflammation and mucus [80]. Inflammation and oedema contribute to wall thickening. Gadolinium-enhanced images may be useful in demonstrating inflammatory change.

Mucous plugging on MRI results in homogeneous high T2-signal intensity in proximal airways or an abnormal branching grape-like pattern more peripherally, equivalent to the tree-in-bud opacities seen on HRCT. In contrast to CT, the improved tissue characterisation of MRI can also differentiate between mucus, haemorrhage and bronchial wall thickening [81]. Air–fluid levels may be identified on MRI, particularly in cystic or varicose bronchiectasis. Unlike CT, using contrast-enhanced MRI sequences, thickened airway walls can be differentiated from mucous plugging. Consolidation may also be identified as high T2-signal inflammatory fluid contrasts with the low airway signal, equivalent to the classical air bronchogram. Air-trapping and mosaic perfusion are not readily seen on conventional proton MRI in the absence of gadolinium (figs 9 and 10).
An early study of 17 CF patients (aged 7–30 years) in 1995 [82] found MRI to be inferior to CT in the assessment of bronchiectasis. Correlations between CT and MRI (r for each observer) were good for bronchial dilation (r=0.81 and 0.50), bronchial thickening (r=0.82 and 0.60) and mucous plugging (r=0.93 and 0.70). Progress in MRI technique in recent years has led to marked improvement in its accuracy. In a study of six paediatric patients with CF, HEBESTREIT et al. [83] found that CXR and MRI provided equal information, and considered MRI suitable for follow-up. In a more recent study in 2007, PUDERBACH et al. [84] evaluated 31 patients with CF using CXR, MDCT and MRI. MRI and MDCT were assessed using a modified Helbich score, whereas CXR was evaluated using a modified Chrispin–Norman score. Mosaic perfusion was excluded from the original scoring system as this cannot be quantified on MRI. They concluded that morphological

Figure 9. a) Transverse magnetic resonance (T2-weighted half-Fourier acquisition single-shot turbo spin-echo (HASTE)) image and b) corresponding computed tomography image in a 14-year-old female with cystic fibrosis. In both images, bronchial wall thickening, bronchiectasis, peripheral mucous plugging and dorsal consolidations are demonstrated, as shown by the arrows. Reproduced from [81] with permission from the publisher.

Figure 10. T1-weighted magnetic resonance imaging showing appearance a) before and b) after contrast medium in a 43-year-old cystic fibrosis patient. The post-contrast images demonstrate extensive bronchial wall enhancement and permit differentiation of a thickened wall from intrabronchial secretions, with intrabronchial fluid having an air–fluid level (arrow). Reproduced from [81] with permission from the publisher.
MRI showed comparable results to MDCT and CXR. Median extent scores for MRI, MDCT and CXR scores were 13, 13.5 and 14, and correlation between modalities ranged 0.63–0.80 (MRI/CT 0.80, \(p<0.0001\); MRI/CXR 0.63, \(p<0.0018\); CXR/CT 0.75, \(p<0.0001\)). The median lobe-related concordance was 80% for bronchiectasis, 77% for mucous plugging, 93% for sacculation/abscesses and 100% for collapse/consolidation.

Montella et al. [85] evaluated patients with primary ciliary dyskinesia using HRCT and MRI. They used a modified Helbich score for both HRCT and morphological MRI assessment, showing mean scores of 12 for both, good-to-excellent agreement between HRCT and MRI scores (\(r>0.8\)), and good correlation between both CT and MRI scores and FEV1 and FVC.

**Functional MRI**

A significant advantage of MRI over CT is its superior ability to assess function. Within the lungs this mainly involves evaluation of haemodynamic function and perfusion and ventilation studies.

**Perfusion imaging**

In the presence of small airways obstruction, regional ventilation defects lead to impaired gas exchange and reflex hypoxic vasoconstriction [86]. Perfusion imaging can thus serve as a marker of airway obstruction. Itti et al. [87] used radionuclide imaging to show that the degree of abnormal lung perfusion correlates well with disease severity in CF, as measured by PFTs and the Shwachman radiographic score. Contrast-enhanced pulmonary MRI imaging can be used to acquire a 3D data set in just 1.5 seconds [88, 89]. This also has advantages over scintigraphy in terms of radiation dose and provides regional information.

Eichinger et al. [90] performed morphological and contrast-enhanced MRI sequences on 11 patients with CF; 198 lung segments were scored for morphological (3 point score of none, moderate or severe) and perfusion defects (0 normal; 1 impaired perfusion). In 86% of segments considered morphologically normal, homogenous perfusion was demonstrated, whereas 97% of segments with severe morphological changes were associated with perfusion defects. Of segments with moderate morphological changes, 53% showed normal and 47% impaired perfusion. Thus contrast-enhanced MRI appears to be a feasible method of assessing regional perfusion defects as a surrogate for small airways disease, although further work is required in order to improve sensitivity in moderately affected areas of lung.

In bronchiectasis, increased blood flow though bronchial and nonbronchial systemic collateral vessels results in a systemic arterial to pulmonary venous shunt. Using conventional proton MRI and phase-contrast flow-sensitive sequences, aortic and pulmonary arterial flow can be readily quantified. In a study of 10 patients with CF and 15 healthy volunteers, Ley et al. [91] found a significantly increased shunt in CF patients (1.3 L·min⁻¹) compared to healthy volunteers (0.1 L·min⁻¹).

Oxygen-enhanced MRI exploits the weak paramagnetic properties of oxygen, which cause a shortening of T1 at high concentration and can be used as a gaseous contrast agent. The solubility of oxygen means that images represent a combination of ventilation and perfusion. A limitation is the low signal-to-noise ratio [81]. Jakob et al. [92] studied five CF patients and five healthy volunteers using oxygen-enhanced MRI, showing inhomogeneity of the lung parenchyma in the CF patients.

**Hyperpolarised noble-gas-enhanced MRI**

Imaging of hyperpolarised noble gases using MRI is a relatively new imaging technique that shows promise in the research arena in the evaluation of several ventilatory functional parameters. Hyperpolarised helium-3 and hyperpolarised xenon-129 are gaseous contrast agents that provide a very high MR signal [35]. Since oxygen promotes depolarisation, the polarised helium-3 is mixed
with nitrogen rather than air before being administered by active inhalation via a device such as a plastic Tedlar bag or respirator-driven gas delivery system. The bag method uses a mixture of 300 mL helium-3 and 700 mL nitrogen and requires a single anoxic breathhold. The respirator-driven system provides an accurate single dose followed by an air chaser and hence no anoxic breathhold is required.

Polarisation is not renewable and has to be used carefully during the scan, with use of sequences to maximise use of finite magnetisation [93]. Dedicated receiver coils for the relevant resonance frequency of helium-3 and xenon-129 are also required.

The different physical properties of helium-3 and xenon-129 present different opportunities. Although helium-3 provides a better signal and greater polarisation levels have been obtained, its larger diffusion coefficient results in signal loss. In addition, although helium-3 is virtually insoluble in water, xenon-129 is highly soluble and hence has potential for use in assessing perfusion [93]. On a purely practical basis, the limited supply of helium-3, estimated at 200 kg globally [94], compared to that of xenon-129 is likely to lead to xenon-129 eventually emerging as agent of choice [95].

The main techniques used in hyperpolarised noble gas imaging are static ventilation imaging and dynamic ventilation imaging, as well as assessment of lung microstructure using ADC and regional oxygen tension imaging.

McMahon et al. [96] showed that static helium-3 MRI ventilation in CF correlated strongly with HRCT assessment of structural abnormalities (R= ± 0.89; p<0.001), and that the correlation was higher between helium-3 MRI and PFT results than helium-3 MRI and HRCT. In a further observational study of 18 patients aged 5–17 years with CF undergoing hyperpolarised helium-2 MRI, van Beek et al. [97] confirmed moderate correlation between a visual score of ventilation on MRI and global assessment of pulmonary function (FEV1 r= -0.41 and FVC r= -0.42).

In a study comparing healthy volunteers and CF patients, Mentore et al. [98] performed spirometry and hyperpolarised helium-3 imaging at baseline in all cases, and following various interventions in the eight CF patients. Treatments in the CF group included bronchodilators, DNase and chest physiotherapy. The number of ventilation defects was scored. The helium-3 ventilation score correlated moderately with spirometry, and was higher in CF patients than controls (mean 8.2 and 1.6, respectively). The helium-3 ventilation score was raised in comparison to controls even in CF patients with normal spirometric results. Defects in the eight treated patients decreased in response to bronchodilator therapy (p=0.025). Woodhouse et al. [99] demonstrated reproducibility of regional and total lung volume measurements using hyperpolarised helium-3 MR in two examinations performed 30 minutes apart in a group of five young CF sufferers.

The ADC of helium-3 or xenon-129 in the lung and the paramagnetic effect of oxygen are two novel methods with the potential for extracting clinically relevant data. The ADC provides a measure of the diffusion of gas and thus an assessment of the degree to which free diffusion is restricted. Helium-3 has a very high self-diffusion coefficient, but, in the lung, diffusion becomes restricted by the boundaries of the airspaces, and thus the ADC can be used to interrogate the microstructure of the lung [93].

The oxygen-induced depolarisation of helium-3 or xenon-129 results in signal decay proportional to the concentration of oxygen [100], permitting estimation of regional oxygen concentration and uptake and regional pulmonary perfusion, and providing a regional ventilation/perfusion (V/Q) map at a much higher resolution than that of radionuclide imaging [101]. Patz et al. [95] measured regional oxygen concentrations using xenon-129, and, although this is inherently more complex than with helium-3 due to diffusion into septal tissue and vasculature, an oxygen tension (PO2) equivalent can be calculated, which can provide valuable functional information.
A limitation of hyperpolarised noble gas MRI is that the signal is also influenced by factors other than ventilation, including the sensitivity of the MR coil and local oxygen concentration in the lung. The need for noble gas isotopes and both polarisation hardware and additional MRI hardware, together with considerable physical and technical support, mean that hyperpolarised noble gas imaging remains expensive and limited to the research environment. However, the potential to perform noninvasive evaluation of regional ventilation, diffusion, regional oxygen concentration, lung microstructure and perfusion without the use of ionising radiation has potential, especially in the research setting.

Summary

MRI has potential in the imaging of bronchiectasis, particularly in conditions such as CF, in which young patients may require serial imaging for disease monitoring and assessment of response to treatment. Compared to HRCT, the ability of MR to provide functional imaging and lack of radiation could compensate for its limited spatial resolution. With improvement in MRI techniques, recent studies have shown good reproducibility and good correlation with PFT results. Further work is required to improve spatial resolution, develop robust validated scoring systems and evaluate correlations with clinical outcomes.

Currently cost, limited availability and limited spatial resolution limit the use of MRI in bronchiectasis largely to the research arena. Although hyperpolarised noble gas imaging has great potential in terms of provision of functional data, technical issues and set-up and ongoing costs suggest its role will be limited to research for the foreseeable future.

Scintigraphy

Prior to the advent of HRCT, ventilation (with or without perfusion) scintigraphy was used to aid disease evaluation in bronchiectasis. DOLLERY and HUGH-JONES [102] studied the physiological implications of bronchiectasis and found reduced blood flow and impaired ventilation in bronchiectatic areas. V/Q scintigraphy typically demonstrates matched ventilation and perfusion defects, reflecting abnormal ventilation secondary to bronchiectasis and associated small airways obstruction [103].

PIFFERI et al. [104] studied 16 children aged 4–18 years with clinical and CXR evidence of bronchiectasis, performing HRCT and V/Q scintigraphy. The extent of bronchiectasis, degree of air-trapping on expiratory HRCT and ventilation and perfusion scores from V/Q scintigraphy were assessed. HRCT scores for bronchiectasis and air-trapping showed a strong correlation with perfusion ($r=0.82$; $p<0.001$) and ventilation scores ($r=0.72$; $p<0.01$). There was a moderate negative correlation between FEV$_1$ and HRCT bronchiectatic scores ($r=-0.53$; $p=0.02$), air-trapping ($r=-0.64$; $p=0.007$) and atelectatic score ($r=-0.54; p=0.03$).

The authors concluded that HRCT provides a comprehensive assessment of children with bronchiectasis, and V/Q scintigraphy and lung function are additive tools to aid diagnosis and guide therapeutic management. The ongoing issue of radiation dose and absence of useful anatomical information, however, limit the value of V/Q scintigraphy in routine practice.

Mucociliary clearance

The interaction between the cilia on respiratory epithelium and the periciliary mucous layer (periciliary liquid (PCL)/overlying mucous layer, together known as the airway surface liquid (ASL) layer, has been widely investigated. Coordinated function is responsible for the constant clearance of foreign material, including microorganisms and other debris, towards the pharynx and ultimate expectoration or swallowing. Impaired mucociliary function has been implicated in many disease processes, but particularly bronchiectasis. Techniques to objectively measure mucociliary clearance (MCC) *in vivo* have been sought in order to improve understanding of the disease processes and evaluate therapeutic response.
Techniques for measuring MCC

*In vivo* assessment of MCC relies on the inhalation of radiolabelled particulate material that becomes trapped in the mucous layer and can be imaged scintigraphically. Data acquired from the gamma camera over time can be presented either as a series of images for visual inspection or, more commonly, as time–activity curves (fig. 11).

Technetium-99m-labelled human albumin, iron oxide and technetium-99–sulfur colloid are some of the aerosols used. Sulfur colloid is nondiffusible, remains extravascular and is expelled by MCC/swallowing. Deposition of particles is affected by many factors. Some, such as particle size and breathing pattern, can be controlled for, whereas others reflect the underlying lung condition (e.g. obstruction and lung size). Thus, in order to make comparisons, it is important to standardise the nature of the aerosolised particles (size and distribution) and provide a consistent nebulised flow in order to produce a reproducible deposition rate [105].

In order to define the margins of the lung and differentiate central (C) and peripheral (P) lung regions, an initial ventilation study utilising a xenon-133 or krypton-81 scan [106] can be performed immediately prior to administration of particulate material. Following this, the patient

**Figure 11.** Measurement of mucociliary clearance (MCC). a) A xenon-133 equilibrium scan was used to identify the left (L) and right (R) lung boundaries in a normal subject, and assign central (C) and peripheral (P) regions of interest (b). c) Deposition image obtained immediately after inhalation of technetium–sulfur colloid in the same subject. d) Mean rate of clearance of technetium–sulfur colloid from 12 subjects with cystic fibrosis at baseline (– – – – –), reflecting clearance from large airways, and slow phase (from 40 minutes to start of cough clearance measurement; -- – – – -- –), reflecting smaller airway clearance, are highlighted. e) Effect of ratio of radioactive counts measured in the C and P regions on rate of MCC, as denoted by particle retention at 120 minutes, in a cohort of normal study subjects. VC: voluntary cough. Reproduced from [105] with permission from the publisher.
inhales nebulised radiolabelled aerosol. Various adjuncts are used during nebulisation in order to provide consistent reproducible dosing, including pneumotachographic devices with visual feedback to control inhalation flow rate and tidal volume within specific ranges, metronomes to guide the timing of inhalation and exhalation, and aerosol dosimetric equipment to pulse aerosol delivery during specific portions of the breathing cycle [105].

Following inhalation, the patient is positioned in front of the gamma camera and the gamma radiation emitted is detected and recorded. The results are analysed graphically with reference to the zones defined on the initial ventilation scan. At this stage of analysis, it is important to account for decay of radioisotope and background radiation level. Given the variability of deposition of radiolabelled aerosol in various parts of the airways, it is important to measure the initial deposition pattern. The deposition pattern is usually presented as a ratio between C and P or as the penetration index (PI), which is the ratio of radioactive counts per pixel in P to counts per pixel in C [107]. A high initial C/P deposition ratio or low PI is associated with a higher clearance rate in the central airways, making this a potential confounding factor in analysing final clearance data.

The rate of clearance from central airways is up to 100–1,000 times faster than that from peripheral airways [108, 109]. A two-phase MCC pattern is typically seen, with an initial rapid phase lasting approximately 30 minutes and reflecting clearance from the central airways and a prolonged slower phase. The latter occurs over 1–2 hours and is thought to represent movement of particles to compartments that are more difficult to clear (e.g. absorption of PCL) or slow clearance from peripheral airway/alveolar deposition. 24-hour measurement of clearance has also been used to assess the pattern of clearance during the slower phase, which could also be of value in assessing response to treatment. This, however, requires a higher administered radiation dose due to the 6-hour half-life of technetium. A static measurement at 24 hours can be used as a marker of deposition in the nonciliate airways or alveoli [110]. The relative contributions to the 24-hour measurement of slow clearance from peripheral airways, alveolar deposition and mixing in a poorly cleared part of the ASL, are not fully understood [105]. The static 24-hour measurement is useful in aiding calculation of other parameters, such as the tracheobronchial retention (TBR) curve, which is derived by subtracting the 24-hour retention from the corrected lung retention (LR) curve.

A potentially more accurate means of assessing peripheral clearance is inhaling particles of different sizes, smaller (4 μm) particles being deposited more peripherally than larger (7.5 μm) ones [111]. Yeates et al. [108] proposed labelling the differently sized aerosolised particles with different radioisotopes to permit simultaneous measurement of central and peripheral regional clearance. This method is not widely used due to practical difficulties.

Some authors [106] advocate measurement of activity solely in the lung periphery, where uptake is more homogenous. This avoids the potential errors caused by differential uptake in central and peripheral airways and confounding by variability of initial deposition. It is, however, limited by a low signal-to-noise ratio due to lower deposition peripherally and intrinsically slower clearance in these regions. It is also not possible to assess response to therapy in the central airways using this method.

Additional imaging following various interventions, such as cough clearance (CC) assessed after a standardised pattern of coughing, can also be performed. This has some limitations, as performing this late in the study makes it less sensitive as the central airways would have been largely cleared of radioisotope. A further normalisation measurement of C/P ratio must be performed prior to CC.

**Clinical applications**

Measurement of MCC has important research applications in both understanding disease processes and assessing therapeutic response. To date, the technique has not been broadly adopted clinically, being cumbersome to establish.
Disorders that impair MCC can seriously affect respiratory function, with build-up of thick mucus in the airways/lungs and inability to expel harmful material. This can predispose to complications, such as infection and structural lung disease. Other factors may influence MCC, which is faster in nonsmokers and enhanced by β2-agonists, particularly in nonsmokers [112].

CF is a prominent example of a condition in which measurement of MCC could prove useful. Scintigraphic evaluation has also been used to demonstrate impaired MCC in primary ciliary dyskinesia [110] and following lung transplantation [113]. There have been limited studies in idiopathic bronchiectasis [114].

In CF, disordered ion transport leads to dehydration of the ASL layer [115], impaired ciliary motion and decreased mucus clearance, ultimately leading to degradation of cilia [105], exacerbating the cycle of frequent infections. Ongoing research is focused on the earliest stages of disease pathogenesis and therapeutic interventions to target defective mucus clearance. Biomarkers objectively measuring MCC have the potential to assess response to treatment at an early stage in contrast to longer-term end-points, such as clinical or functional parameters, and thus to expedite drug development.

In a study of 24 patients with CF, DONALDSON et al. [116] showed improved MCC, measured using technetium-99-labelled iron oxide, at both 1 and 24 hours after inhalation of hypertonic saline, and that pretreatment with amiloride reduced the magnitude of this improvement. Using radiolabelled iron oxide BENNETT et al. [106] demonstrated significantly reduced baseline MCC at 40 minutes in CF patients compared to healthy volunteers. In the CF group, treatment with uridine 5′-triphosphate and amiloride in combination improved peripheral MCC to near-normal levels. Similar studies have used technetium–sulfur colloid to demonstrate improved MCC and CC following inhaled hypertonic saline and mannitol in CF patients [117].

In summary, MCC can be measured using radiolabelled particulate materials, such as technetium-99–sulfur colloid. In the research setting, this provides a potential biomarker for evaluation of mucociliary dysfunction and, in particular, assessment of the impact of targeted therapies. This is especially true in conditions such as CF, in which impaired MCC plays a significant part in the pathophysiology of the disease and where treatment is targeted at improving this.

Conclusions

Imaging plays a central role in the diagnosis, characterisation and quantification of disease severity in bronchiectasis, as well as the evaluation of complications. Currently CXR and CT are the main modalities. CXR is the initial screening tool, but has well-documented limitations in sensitivity and specificity, particularly in early disease. Radiography also plays an important role in the diagnosis of complications. HRCT is the reference standard in identifying airway dilation, permitting detection of disease and quantification of extent. Routine surveillance CT has potential for the diagnosis of structural disease at an early stage and impact on patient care, particularly where these is discordance with functional parameters. Radiation dose, however, remains an area of concern requiring further elucidation, particularly in the cohort of CF patients given their ever-increasing life expectancy and the potentially large cumulative radiation dose. Although the present review concentrates on the monitoring of disease, CT is an excellent problem-solving tool, permitting the diagnosis of both infective complications, such as abscess, empyema and aspergilloma, as well as identification of small pneumothoraces or enlarged systemic collateral vessels (fig. 11) and aiding relevant image-guided intervention.

MRI offers opportunities to image the lung structure and its function without the use of ionising radiation. The spatial resolution is inferior to that of CT but has improved substantially over recent years. An increasing role for structural (proton) MRI is anticipated, but widespread adoption will require further evidence to support its effectiveness. Although hyperpolarised noble gases permit interrogation of a range of physiological parameters, the set-up costs of this technique
are likely to ensure it remains a predominantly research tool for at least the foreseeable future. Evaluation of MCC using scintigraphy is another area in which there is great potential, particularly in order to expedite and reduce costs of drug development.

**Statement of interest**

None declared.

**References**


et al.


49. Logan PM, Muller NL. High-resolution computed tomography of the chest in bronchiectasis. Eur Radiol 2004; 14: 593–596.


