It is important to differentiate chronic thromboembolic pulmonary hypertension (CTEPH) from other forms of pulmonary hypertension (PH) to target treatment and optimize therapeutic outcome. Misdiagnosis is common, and high-quality imaging is essential if CTEPH is to be diagnosed correctly. In addition to making a diagnosis, imaging helps identify patients for surgery, aids surgical planning, and provides postsurgical monitoring. Ventilation-perfusion scintigraphy and pulmonary angiography have been the mainstay of diagnosis and surgical assessment for many years, but cross-sectional techniques are rapidly taking over. Echocardiography is used to confirm or refute the presence of PH and to identify cardiac causes if PH is present. For patients with PH but no evidence of cardiac disease, multislice computed tomography (CT) is the next best step. CT distinguishes CTEPH from idiopathic arterial PH, evaluates underlying lung disease, and may help identify rarer causes of PH. CT is quick, widely available, and inexpensive. There is, however, a significant radiation burden, and it is unsuitable for serial examinations. Magnetic resonance (MR) involves no ionizing radiation and makes an ideal alternative. When combined with techniques for measuring ventricular function and blood flow, MR provides unique insight into structure and function. CT and MR are complementary techniques, and together they represent the future of imaging in PH. How they might be used in routine clinical practice is presented as a diagnostic algorithm developed at Papworth Hospital, the United Kingdom’s national center for surgical treatment of CTEPH.

**Keywords:** chronic thromboembolic pulmonary hypertension; computed tomography; diagnosis; echocardiography; magnetic resonance angiography

Misdiagnosis in chronic thromboembolic pulmonary hypertension (CTEPH) is common because patients often present with subtle or nonspecific symptoms. Clinical presentation typically follows one of two scenarios: (1) progressive dyspnea on exertion, hemoptysis, and/or signs of right heart dysfunction (e.g., fatigue, palpitations, and syncope) or (2) pulmonary hypertension after single or recurrent episodes of overt pulmonary embolism (PE) (1).

Many patients experience a “honeymoon period” between the acute event (PE) and the development of overt signs or symptoms. This may last from months to many years and may mask the diagnosis. Lang (2) suggested that up to 63% of patients give no history of acute PE. In these patients, the clinical course of CTEPH is often indistinguishable from other types of pulmonary hypertension (PH), in particular idiopathic pulmonary arterial hypertension (IPAH), where symptoms may be just as severe. Accurate diagnosis is essential if treatment is to be targeted and outcome optimized.

Imaging has become central to the diagnosis of CTEPH and in monitoring subsequent treatment. Although a variety of imaging modalities are available and of proven value, there is no benefit in using every test on every patient. This article describes a rational approach to imaging in PH, how it is used in the diagnosis of CTEPH, and how it is used to assess operability when CTEPH is present. All the techniques described are well established and form part of the routine imaging regime used at Papworth Hospital, the United Kingdom’s national center for surgical treatment of CTEPH.

**IMAGING IN CTEPH**

**Initial Work-up**

Patient evaluation must establish the presence and severity of PH, identify its etiology when present, and, if thromboembolic disease is the cause, determine whether surgical intervention is appropriate. Initial work-up includes physical examination, pulmonary function testing, and chest radiography. Findings from the initial work-up usually indicate whether the patient’s symptoms are cardiac, pulmonary, or pulmonary-vascular in origin.

Patients with a normal chest X-ray and a low likelihood for disease need no further investigation. Patients with a normal chest X-ray and a strong history or a chest X-ray abnormality suggesting PH (e.g., cardiomegaly, pulmonary vascular abnormality) should be investigated by echocardiography.

**Echocardiography**

Transthoracic echocardiography establishes whether resting PH is present (estimate of pulmonary artery systolic pressure from peak Doppler velocity of tricuspid regurgitant jet). It also assesses the right ventricle (RV) and left ventricle (LV), assesses valve integrity, and examines overall cardiac anatomy for underlying cardiac causes of PH (e.g., congenital heart disease or valve disease). Depending on the stage of disease, atrial and ventricular enlargement, RV and LV impairment, tricuspid regurgitation, flattening and displacement of the interventricular septum, and pericardial effusion may be seen (3). If no cardiac cause for PH is found, other imaging is needed.

Up to 1% of patients with acute PE go on to develop CTEPH, although this is an area of controversy because many believe that there is a higher prevalence (4). Routine echocardiography 6 wk after PE has therefore been suggested as a screening tool to identify patients with persistent PH and/or RV dysfunction (5). The ideal timing of the examination, the need for long-term follow-up, whether it should be targeted to symptomatic or asymptomatic patients, and its cost-effectiveness overall has yet to be determined.

**Ventilation–Perfusion Scanning**

For many years, ventilation-perfusion (V/Q) scintigraphy has been the mainstay of diagnosis in PE. It can reliably distinguish between large-vessel occlusive disease and small-vessel pulmonary vascular disease, and a normal V/Q scintigram virtually rules out CTEPH (1, 6–9). In patients with PH, one or more mismatched segmental or larger defects generally indicates
CTEPH (8). A normal perfusion study or the presence of multiple, small, subsegmental defects make IPAH or another form of small-vessel PH more likely (6). Occasionally, multiple mismatched defects are seen in pulmonary venoocclusive disease, pulmonary capillary hemangiomatosis, fibrosing mediastinitis, pulmonary vasculitis, or pulmonary artery sarcoma (1, 10–13).

**Computed Tomographic Angiography**

At Papworth Hospital, V/Q scintigraphy has been largely superseded by multislice computed tomography (CT). Remy-Jardin and colleagues (14) were the first to show that spiral CT reliably demonstrates thromboemboli in second- to fourth-order pulmonary vessels and could therefore replace V/Q scintigraphy in suspected PE. Even then, with a single-slice CT scanner and volume coverage limited to segmental vessels, the negative predictive value of pulmonary CT angiography (CTA) for acute PE was 99% (15). With the advent of multislice CT and resolution approaching 0.5 mm in all planes, results for CTA match those obtained with conventional pulmonary angiography (16, 17). The difference is that CTA is a three-dimensional technique. The role of pulmonary angiography in providing a surgical “road map” (18–20) is gradually being lost to cross-sectional methods. Pulmonary CTA shows luminal thrombi, organized mural thrombi, occlusions, and webs, just as might be seen with conventional angiography (21) (Figure 1). It is, however, noninvasive and a fraction of the price of conventional angiography.

CT provides more than a vascular map. High-resolution CT (HRCT) of the lung shows a mosaic pattern in CTEPH that is virtually diagnostic (Figure 2) (22–25). The only important mimic is air trapping, which can be seen in a variety of small-airway diseases. The distinction is usually straightforward, but if the clinician is in doubt, expiratory images discriminate between the two. HRCT is also helpful identifying other causes of PH. A nodular ground-glass pattern is frequently seen in IPAH, IPH-CREST (limited systemic sclerosis syndrome), and capillary hemangiomatosis. The HRCT features of these conditions show considerable overlap, and a specific diagnosis can rarely be made; however, CTEPH can be differentiated from small-vessel PH. Venoocclusive disease is distinct from other small-vessel diseases in that its ground-glass nodules are frequently associated with interlobular septal thickening (26) (Figure 3). Mediastinal adenopathy is a nonspecific but well recognized feature of IPAH, capillary hemangiomatosis, and venoocclusive disease. It is not usually seen in CTEPH and, if it is present, raises the possibility of associated small-vessel disease or other causes of lymphadenopathy.

The timing of the intravenous contrast bolus for CTA should opacify pulmonary and systemic circulations. This allows assessment of all cardiac chambers and the pulmonary vascular tree. Although often ignored on chest CT, a number of cardiac features should be looked for as follows (27):

- Cardiac chamber size
- Position and shape of the interventricular septum
- The presence or congenital cardiac abnormalities
- Anomalous pulmonary venous drainage
- Contrast reflux into the inferior vena cava (IVC) and hepatic veins indicating the presence and severity of tricuspid regurgitation (28)
- Size and distribution of bronchial arteries and nonbronchial systemic arteries

RV dilatation is easily assessed by CT, even without ECG gating. Comparing RV and LV diameters at midventricular level, an RV/LV diameter ratio greater than 1:1 indicates RV dilatation.

Figure 1. Selective left pulmonary angiogram (A) and matching three-dimensional reconstruction from a computed tomography (CT) pulmonary angiogram (B) in a patient with chronic thromboembolic pulmonary hypertension (CTEPH). Tight webs, typical of CTEPH, are shown on the conventional angiogram and CT angiogram (arrows).
Figure 2. High-resolution CT in a patient with CTEPH showing mosaic perfusion (A). Areas of pulmonary hyperperfusion are of high attenuation (dark arrows) and are associated with large vessels, whereas areas of hypoperfusion are of low attenuation and contain small vessels. Coronal reconstruction of the lung parenchyma from a patient with CTEPH (B) shows that hyperperfused areas (arrows) correlate well with regions of residual perfusion seen on perfusion scintigraphy (C).

Figure 3. High-resolution CT in idiopathic pulmonary arterial hypertension (A) and venoocclusive disease (B). In both conditions, there may be ground-glass nodular shadowing tending to coalescence. Venoocclusive disease is also associated with smooth interlobular septal thickening (black arrows), mimicking left ventricular failure.

(Figure 4) (29). Planimetry of the RV blood pool on axial slices has also been shown to give an accurate estimate of diastolic volume when compared with that obtained by magnetic resonance (MR). Although the majority of patients with valve disease
Figure 4. CT images through the right ventricle (RV) in a patient with CTEPH before (A) and 3 mo after pulmonary thromboendarterectomy (B). Preoperatively, RV is dilated with right ventricular/left ventricular (RV/LV) ratio $\gg 1$ and a small pericardial effusion (white arrows). Pericardial effusions are common in pulmonary hypertension and carry a poor prognosis. After surgery, RV returns to normal, and LV regains its normal shape. The RV/LV ratio is normal at 1.0.

or a congenital abnormality are identified on echocardiography, sinus venous arterial septal defect (ASD), patent ductus arteriosus, and anomalous pulmonary venous drainage can be missed. It is important to look for these conditions even though previous echocardiography may have been negative. Bronchial artery dilatation is a well-recognized feature of CTEPH on conventional angiography (30) and has recently been described on CTA (31, 32). Identifying bronchial artery dilatation is important because a large bronchial blood supply can complicate surgery, and its presence has been reported to be an indicator of poor surgical outcome.

**MR Angiography**

Contrast-enhanced MR angiography (CEMRA) is an established alternative to CTA in all vascular beds beyond the coronary tree. Because no ionizing radiation is involved, the technique is ideally suited to young patients and those requiring serial assessment (e.g., for postoperative follow-up). The typical findings of CTEPH (intraluminal webs and bands, vessel cutoffs, and organized central thrombus) are well demonstrated and can be seen in vessels to segmental level (Figure 5). Beyond the segmental level, the higher spatial resolution of conventional angiography makes it superior. Does this matter? Surgical intervention is largely limited to proximal and segmental vessels, and in a study by Kreitner and colleagues (33), CEMRA correctly predicted surgical success in 33 of 34 patients. Pulmonary MRA also correlates well with CTA, but beyond the segmental level the higher spatial resolution of CTA makes CTA superior (25, 34). Pulmonary MRA has similar accuracy to V/Q scintigraphy in distinguishing between patients with CTEPH and IPAH (35).

As with CT, there is more to MR than MRA. Pulmonary MRA may be combined in the same examination with a variety of cine techniques to gauge cardiac function and flow. Cine imaging allows qualitative and quantitative assessment of ventricular function. Using planimetry of contiguous cine slices, end-systolic volume, end-diastolic volume, stroke volume, ejection fraction, and muscle mass can be determined. Numerous studies have shown these measurements to be accurate and reproducible, and, over recent years, MR has become the gold standard for determining RV and LV function (36, 37).

Phase-contrast velocity mapping is the MR equivalent of Doppler ultrasound. It has the advantage that it is independent of acoustic window and can measure absolute vessel flow in addition to mean or peak velocity. In the setting of PH, its most important applications include measurement of cardiac output and pulmonary and systemic flow measurements in the estimation of right-to-left and left-to-right shunts. In patients with CTEPH, phase-contrast imaging has been used to measure flow in the ascending aorta and right and left pulmonary artery before and after pulmonary thromboendarterectomy (PEA). As might be expected from the ease of surgical access, postoperative blood flow in the right main pulmonary artery increases significantly more than left. The size of the bronchial artery shunt also falls after surgery; the levels of decrease corresponding broadly to the extent of revascularization (38).

Our experience at Papworth mirrors that described previously. As a consequence, pulmonary MRA has replaced conventional angiography as the surgical “road map” in patients being considered for surgery. This has the added benefit that the preoperative examination serves as a baseline for noninvasive postoperative follow-up of pulmonary vascular anatomy and cardiac function. When MR is contraindicated, CT is used.

**Pulmonary Angiography**

Pulmonary angiography predates all the other techniques described and has been the cornerstone of managing patients with CTEPH for many years. By identifying occlusions and intravascular webs, it confirms the diagnosis and gives an indication of operability (18–20). Limited access, limited expertise, and a small but definite patient risk favor newer, noninvasive methods. At Papworth, pulmonary angiography is performed only in patients being considered for PEA when an adequate surgical road map has not been provided by CT or MR. In this situation, it is best performed at the surgical center where it can be added to a right-heart catheter examination with little additional risk. If pulmonary angiography has to be done, two views of each lung are essential to show pulmonary vascular anatomy in sufficient detail for surgical planning.
Pulmonary Angioscopy

Pulmonary angioscopy was developed in an era before CT and MR as an adjunct to the preoperative evaluation of CTEPH (39). It is invasive and expensive and carries a small but definite risk. It is debatable whether this technique would have developed had current noninvasive cross-sectional techniques been available at the time. Nonetheless, angioscopy provides excellent views of chronic organized emboli and the intimal surface and can identify bands or webs across the vascular lumen as a consequence of recanalization (39). Intimal plaques are nonspecific and are seen in all types of PH, their extent and severity correlating with the level of PH, much as systemic atheroma may relate to hypertension.

Depending on the expertise of the surgical center, angioscopy is performed in up to 30% of patients with CTEPH being considered for PEA. Although it has been shown that angioscopy can predict hemodynamic outcome in patients with relatively mild PH and can confirm operability in patients with severe PH (40), noninvasive methods providing similar information are increasingly becoming available.

CLINICAL CONDITIONS MIMICKING CTEPH

CTEPH is often misdiagnosed, and the true diagnosis may not be made until autopsy (4). Table 1 lists some of the conditions that mimic CTEPH and describes the imaging features that may help in identifying them.

DIAGNOSING CTEPH: THE PAPWORTH ALGORITHM

Imaging is central to making the diagnosis and management of CTEPH, but which test do you use, and when? The imaging algorithm used at Papworth for CTEPH diagnosis is shown in Figure 6. All the techniques described, with the exception of angioscopy, are in routine use.

In summary, patients presenting with suspected PH have a chest X-ray. Those with abnormal X-rays and those with normal X-rays but a strong clinical history undergo echocardiography. If PH is confirmed on echocardiography and no cardiac cause is found, CTA is performed. This identifies CTEPH, lung disease, and a variety of unsuspected shunts. If none of these is present,

TABLE 1. OVERVIEW OF CONDITIONS THAT MIMIC CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION AND DIAGNOSTIC FEATURES THAT MAY HELP IN THEIR DIAGNOSIS

<table>
<thead>
<tr>
<th>Conditions Mimicking CTEPH</th>
<th>Techniques Used for Diagnostic Differentiation</th>
</tr>
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<tbody>
<tr>
<td>Fibrosing mediastinitis causing obstruction of the pulmonary veins and arteries</td>
<td>Chest X-ray is rarely helpful. CT shows mediastinal soft tissue obliterating fat planes and encasing and compressing vascular structures (41).</td>
</tr>
<tr>
<td>Pulmonary artery sarcoma</td>
<td>Echocardiography, CT angiography, and MR have difficulty distinguishing sarcoma from central thrombus. Sarcoma may involve the pulmonary valve and extend retrogradely into the RV infundibulum, unlike thrombus (42, 43). Contrast-enhanced MR may show tumor enhancement, whereas thrombus will not (44).</td>
</tr>
<tr>
<td>Large-vessel arteritis (or Takayasu’s arteritis)</td>
<td>Pulmonary angiography, angioscopy, and aortography may not be helpful. Cross-sectional CT or MR may identify concentric inflammatory mural thickening. FDG-PET shows intense uptake in active disease (45).</td>
</tr>
</tbody>
</table>

Definition of abbreviations: CT = computed tomography; FDG-PET = fluorodeoxyglucose positron emission tomography; MR = magnetic resonance; RV = right ventricular.
HRCT often shows features suggesting IPAH, venoocclusive disease, or papillary hemangiomatosis. V/Q scintigraphy is not routinely used. Although it can differentiate between CTEPH and IPAH, it does not help in identifying other causes of PH, such as unsuspected shunts, large-vessel pulmonary arteritis, and primary pulmonary vascular tumors. If necessary, pulmonary angiography and MR are used to problem-solve or to provide a surgical road map in patients considered suitable for surgery.

CONCLUSIONS
CT, in combination with MR, represents the future for diagnosis and management of patients with CTEPH. Both techniques detect postembolic obstructions at the lobar and segmental levels, although at the subsegmental level the spatial resolution of CT is superior to MR. Not every patient with PH has CTEPH; imaging must identify patients with CTEPH, but it must also provide alternative diagnoses when other causes of PH are present.

Because multislice CT and cardiac-enabled MR scanners are widely available, the proposed imaging algorithm should be achievable in most hospitals. CT and MR have not reached the peak of their development. Stress ventricular function imaging, pulmonary flow waveform analysis, and MR lung perfusion are just some of the techniques waiting to be explored further. We are hopeful that as we move forward in our understanding of CTEPH, we will no longer have to wait until autopsy to make a diagnosis.

Conflict of Interest Statement: R.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

References

Figure 6. Algorithm used at Papworth Hospital for the investigation of suspected pulmonary hypertension. CXR = chest X-ray; Echo = echocardiogram; IPAH = idiopathic pulmonary arterial hypertension; L = left; PH = pulmonary hypertension; R = right.


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