Diagnosis and Preoperative Evaluation of Chronic Thromboembolic Pulmonary Hypertension

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Chronic thromboembolic pulmonary hypertension (CTEPH) can be defined as precapillary pulmonary hypertension (PH) as assessed by right heart catheterization, and results from incomplete resolution of the vascular obstruction associated with acute pulmonary embolism (PE). Pulmonary thromboendarterectomy (PTE) is the therapy of choice for CTEPH patients with surgically accessible thrombi.
Although associated with potential risks, PTE has been found to improve, and in many cases normalize pulmonary hemodynamics, functional status, and long-term survival. It is critical to undergo careful diagnosis and preoperative selection of patients who will most likely benefit from surgery. We have used published literature along with our personal experiences to review diagnosis of CTEPH and evaluation in advance of the PTE procedure.
In patients with PH or suspected PH, a complete diagnostic workup should be performed to identify the underlying etiology of the disease. Pulmonary angiography and right heart catheterization are the preferred assessment tools to diagnose CTEPH. PTE remains the treatment of choice, and for further evaluation of operability and preoperative risk patients should be referred to a CTEPH expert center.

Chronic thromboembolic pulmonary hypertension (CTEPH) results from incomplete resolution of the vascular obstruction associated with acute pulmonary embolism (PE).[1,2] CTEPH can be defined as precapillary pulmonary hypertension (PH) as assessed by right heart catheterization, ie, mean pulmonary arterial pressure (mPAP) ≥25 mm Hg and pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg, in the presence of multiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries after at least 3 months of effective anticoagulation.[3] CTEPH is considered to develop in 1% to 4% of patients who survive an acute PE.[1] In a recent prospective study in patients with newly diagnosed CTEPH, a history of acute PE was confirmed in 74.8% of the patients included.[4] In CTEPH patients without evidence for a previous acute PE episode, clinical risk factors that have been identified for developing CTEPH include ventriculoatrial shunt, indwelling catheters and leads, splenectomy, thyroid replacement therapy, inflammatory bowel disease, and a history of malignancy.[5,6] Abnormalities in coagulation and fibrinolysis pathways have been associated in the minority of CTEPH patients, with the most prevalent ones being lupus anticoagulant and antiphospholipid antibodies.[7] Increased levels of factor VIII, which is a risk factor for recurrent PE, have been shown to be present in patients with CTEPH as compared to healthy subjects and patients with other forms of PH.[8]

If left untreated, CTEPH is a progressive and life-threatening disorder, with survival being proportional to the degree of PH at the time of diagnosis.[9,10] Over time, a gradual hemodynamic and symptomatic decline can be observed in CTEPH patients, which appears to be related to the development of a secondary pulmonary hypertensive arteriopathy in the small nonobstructed precapillary pulmonary vessels.[11] As a consequence, prognosis is in major part determined by the progression of this arteriopathy.[12]

Pulmonary thromboendarterectomy (PTE) is the therapy of choice for CTEPH patients with surgically accessible thrombi, which essentially offers a chance to cure the disease.[1,13] PTE has been found to improve, and in many cases normalize pulmonary hemodynamics, functional status, and long-term survival. The surgery, however, does not come without potential risk. Reported peri- and direct postoperative mortality vary between PTE centers, with 2% to 3% even in the most experienced centers.[13,14] Therefore, it is critical to undergo careful diagnosis and preoperative selection of patients who will most likely benefit from surgery.

CLINICAL PRESENTATION

Most CTEPH patients present with gradually progressive exercise intolerance, typically portrayed as exertional dyspnea, fatigue, palpitations, and/or a nonproductive cough. Occasionally, patients may present with hemoptysis originating from hypertrophied bronchial arteries.[15] The exercise intolerance is in major part caused by the inability of the heart to sufficiently increase pulmonary blood flow due to a decreased right ventricular (RV) stroke volume response during exercise.[16,17] As blood flow fails to perfuse the ventilated lung, dead space ventilation will increase; to compensate

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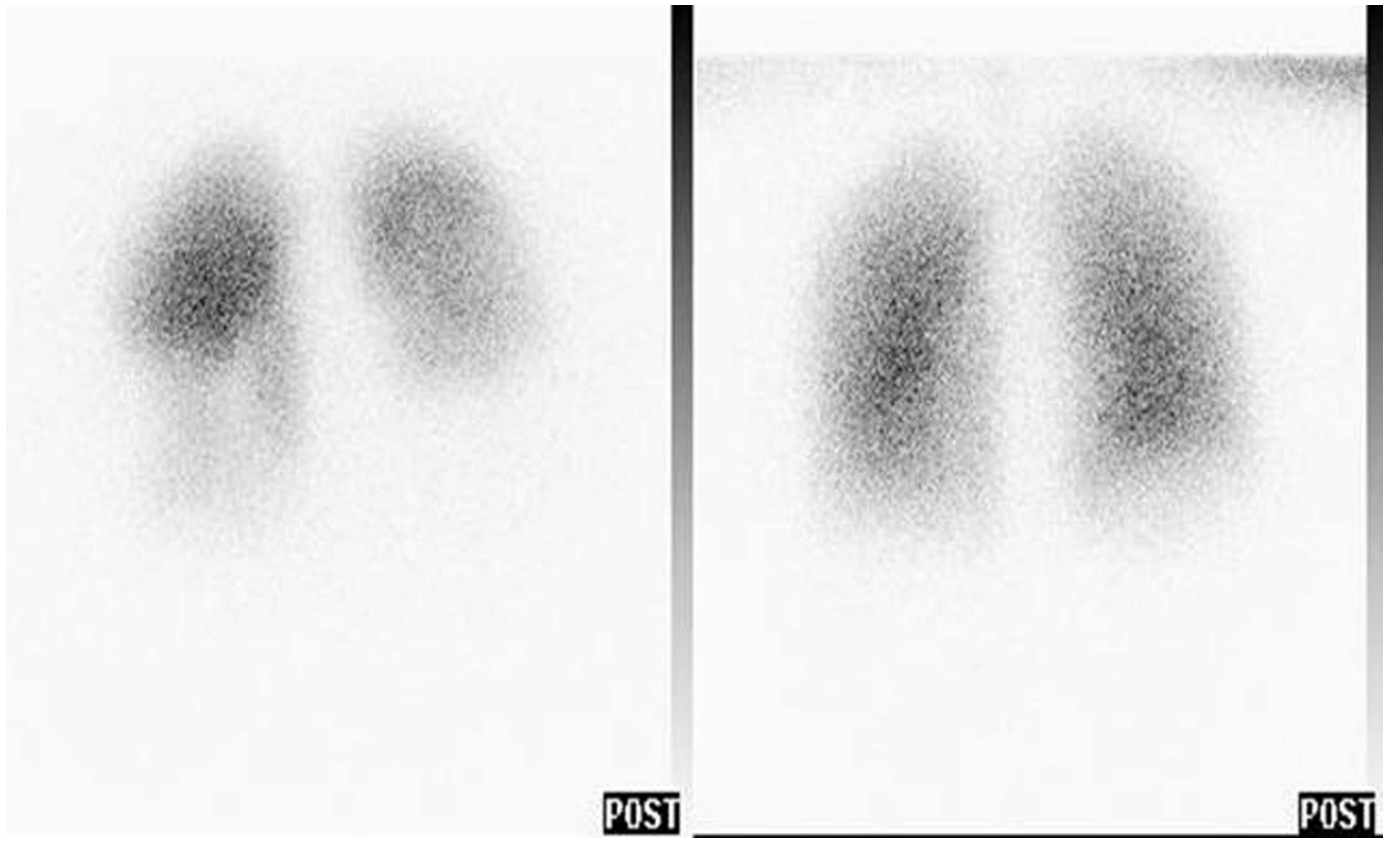

Figure 1: Ventilation/perfusion scintigraphy (posterior view) in a patient with chronic thromboembolic pulmonary hypertension demonstrating absent perfusion (left) of the middle lobe, and the right and left lower lobes, while ventilation is normal (right).

for this increase the patient's ventilatory requirement must increase. At the same time, the inability to increase cardiac output impairs oxygen transport appropriately in response to exercise, causing a low work rate "lactic acidosis" and exercise-induced hypoxemia, both further stimulating the ventilatory drive.[18] In more advanced stages of disease there may be signs of RV failure, chest pain on exertion, and syncope. The ensuing progressive RV failure leads to worsening disability and early death.[11]

On physical examination of the heart, prolongation of the second heart sound with a fixed accentuated P2 is characteristic for a late closure of the pulmonary valve due to RV overload; a tricuspid insufficiency murmur is often present. Over the lungs in approximately 30% of patients a bruit can be heard, representing flow turbulence in the compromised, partially occluded pulmonary vessels.[11] This pulmonary flow murmur is a finding specific to CTEPH, not seen in other forms of PAH. Evaluation of ECG can show signs of RV overload, which include right axis deviation and T-wave inversion in V1-V5.[9]

Chest x-ray is remarkably normal in many CTEPH patients. In a more advanced state of the disease, enlargement of the proximal pulmonary vasculature can be observed; depending on the arteries involved, this finding can be asymmetric. Also, signs of right heart chamber enlargement, such as an enlarged right heart border and obliteration of the retrosternal space may be observed. The parenchyma of the lung may show areas of relative hypoperfusion or may show evidence for previous lung infarction.[19]

Pulmonary function testing does not show a specific CTEPH pattern. Lung volumes and spirometry are generally within normal limits. Diffusion capacity for carbon dioxide may be normal or slightly reduced. It is, however, of use in the preoperative workup, evaluating coexisting emphysema or interstitial lung disease.

DIAGNOSTIC WORKUP OF CTEPH

The diagnostic workup and preoperative evaluation in patients suspected to suffer from CTEPH are based on 3 pillars: 1) the presence of PH and chronic thromboembolism needs to be established and the hemodynamic severity of the disease must be determined; 2) the operability in terms of surgical accessibility of the chronic thromboemboli needs to be assessed; and 3) a thorough preoperative risk assessment must be made. Transthoracic echocardiography is of major importance to define the presence and severity of the PH.[3] The echocardiogram typically demonstrates variable degrees of RV dilatation and hypertrophy. The interventricular septum may be flattened and often exhibits paradoxical motion, with encroachment of the septum into the left ventricle. Variable degrees of tricuspid regurgitation can be present. The peak systolic pulmonary artery pressure (sPAP) can be estimated using the modified Bernoulli equation.[20] A

shortened pulmonary acceleration time can give additional information on elevated pulmonary pressures.[21] Echocardiography may also demonstrate the presence of a patent foramen ovale, an atrial or ventricular septal defect, or concomitant left heart disease. Exercise characteristically increases PH in these patients. Therefore, in patients with only mild abnormalities at rest, performing exercise echocardiography has been suggested to assess hemodynamic response to activity. However, the application and utility of exercise echocardiography in diagnosing PH still needs confirmation by prospective studies.[3,22]

Radioisotope ventilation-perfusion (V/Q) scintigraphy is absolutely essential to the diagnostic evaluation of PH and is the most crucial test in determining the presence of thromboembolism. A normal V/Q scan practically rules out chronic thromboembolic disease as cause of PH. In CTEPH patients, it typically shows multiple lobar and/or segmental perfusion defects (Figure 1). Perfusion scintigraphy, however, tends to underestimate the degree of vascular obstruction. Therefore, in the workup of patients with PH, an equivocal scan needs further evaluation by pulmonary angiography.[23,24] It should be emphasized that there is no substitute for the V/Q scan in the diagnosis of CTEPH with its near 100% sensitivity. However, indistinguishable patterns of V/Q defects have been reported in patients with extrinsic pulmonary vascular compression from mediastinal lymphadenopathy or fibrosis, primary pulmonary vascular tumors, and large-vessel pulmonary arteritis.[25] V/Q scintigraphy in case of distal pulmonary vascular disease most frequently will show a mottled appearance, with the exception of pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis, in which the perfusion scan may show lobar and/or segmental defects.[26,27]

If chronic thromboembolism is considered to be present, pulmonary angiography is mandatory to confirm the presence of PH and to establish its chronic thromboembolic nature. Moreover, it is used to determine whether the chronic thromboembolic obstruction is surgically accessible. When

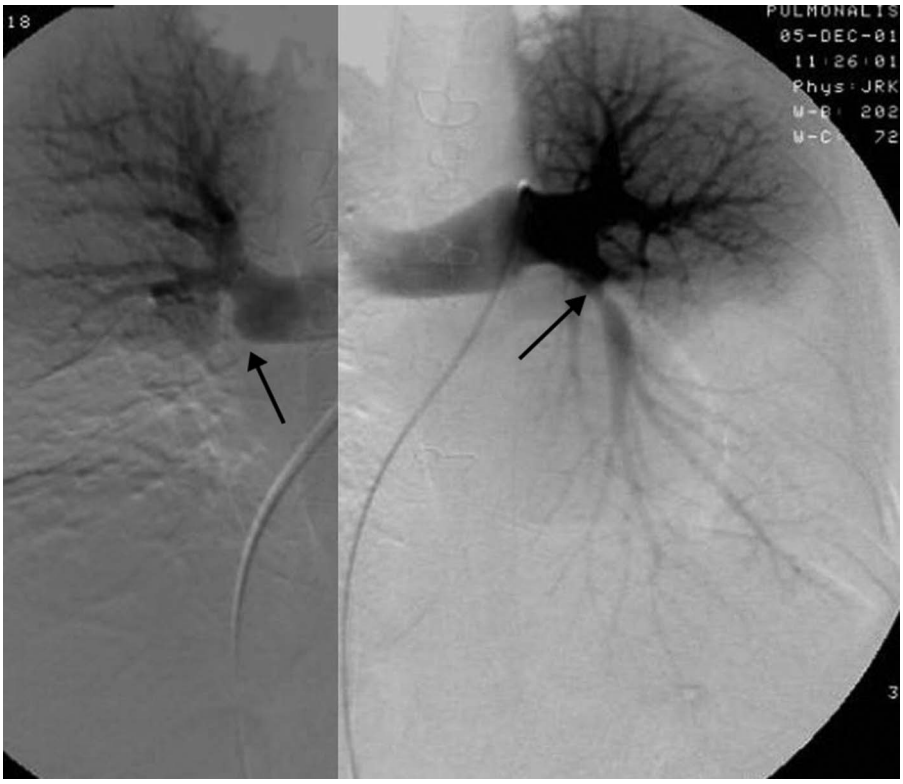

Figure 2: Right and left pulmonary angiography in the patient from Figure 1, demonstrating occlusion of the pulmonary arteries to the middle lobe and the right and left lower lobes due to chronic thromboembolism manifesting as pouches (black arrows).

biplane angiography is performed, this will in the majority of cases provide adequate information on lobar and segmental anatomy to determine the surgical accessibility. Angiographic findings in CTEPH differ from the findings in acute PE. In CTEPH, the radiographic abnormalities reflect different patterns of organization and recanalization of emboli. Pouches, stenosis with or without post-stenotic dilatation, intimal irregularities, webs, and bands are the classic angiographic abnormalities seen in CTEPH (Figure 2). Pulmonary angiography can be combined with right heart catheterization to establish the hemodynamic severity of disease, and it provides essential information on cardiac function. In addition, measurements of oxygen saturations in the vena cava, right heart chambers, and the pulmonary artery may reveal previously undetected intracardiac shunting. In patients at risk for coronary artery disease, simultaneous coronary angiography should be considered, as combining coronary artery bypass grafting with PTE, as well as valve repair, can be performed in most patients with similar perioperative risk.[28]

Although the combined "classic" biplane pulmonary angiography with right heart catheterization are considered the gold standard for diagnosing CTEPH in most expert centers, some of the recently developed diagnostic modalities are also utilized to provide additional information. Contrast-enhanced computed tomography (CT) angiography is performed, as it may add information on vascular obstructions in the main stem of both pulmonary arteries, which can be missed by conventional angiography (Figure 3). It also provides additional information on the lung parenchyma and mediastinal structures, so can be used to study the presence of other conditions which may mimic chronic thromboembolism.[29,30] In CTEPH, CT angiography may show organized thrombi in the (proximal) pulmonary arteries, abrupt tapering of vessels, intimal irregularities, and webs. In addition, next to the PH-associated dilatation of the central pulmonary arteries and right heart chambers, post-PE scarring in underperfused lung areas can result in a mosaic pattern of perfusion

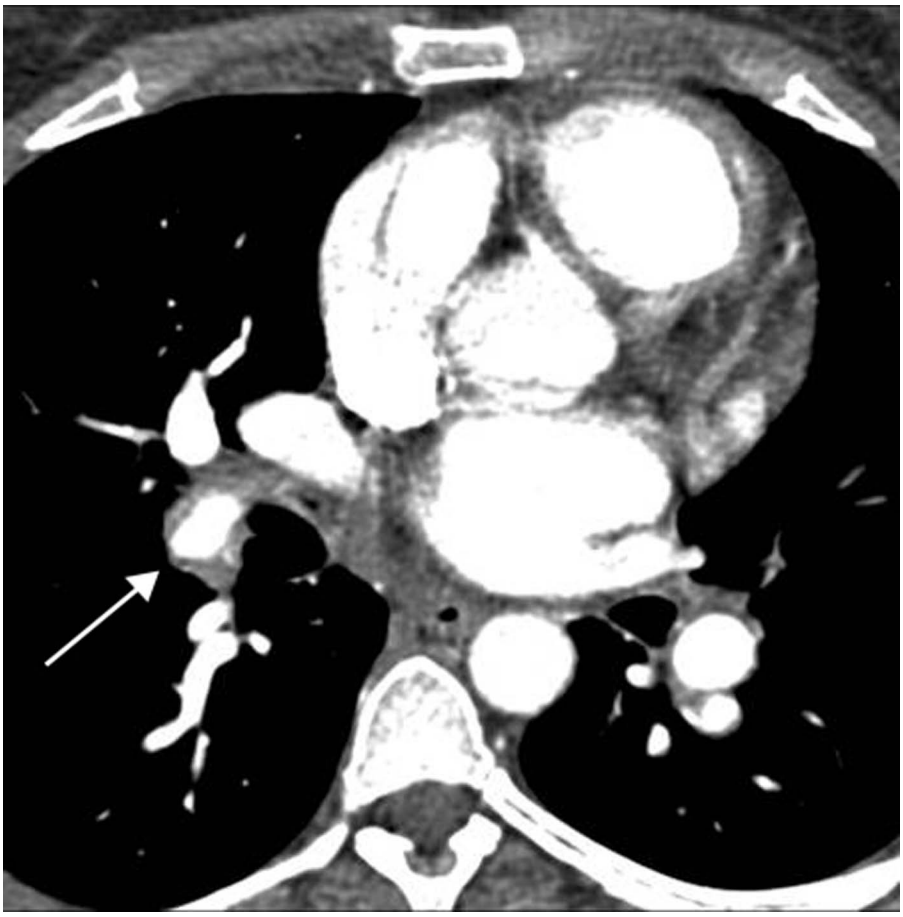

Figure 3: Contrast-enhanced helical multidetector CT image of a patient at the level of the right main pulmonary artery, showing a wall-adherent chronic thrombus.

and the presence of collateral vessels arising from the bronchial arterial circulation that point to the diagnosis.[31,32] In CTEPH patients, the presence of dilated bronchial artery collaterals was shown to be associated with a better postoperative outcome, ie, a lower postoperative pulmonary vascular resistance (PVR) and a lower mortality.[33]

The most recent CT modalities, combined with the increase in experience using the technique, show favorable sensitivity levels in evaluating CTEPH. While promising, V/Q scan is the test of choice to definitely "rule out" and diagnose CTEPH. Further prospective confirmation is needed before recommendations can be given regarding the utility of the CT.[34,35] A radiographic pitfall of particular interest that can be appreciated on CT angiography is "nonobstructive in-situ pulmonary artery thrombosis," which may occur in idiopathic pulmonary arterial hypertension (PAH) and may mimic pulmonary artery occlusion due to chronic thromboembolic disease. Operative removal of these clots must be avoided since it will not result in hemodynamic improvement.[36] It is recommended that if there is a question regarding whether the findings represent CTEPH or PAH with thrombus in situ, the images should be referred for review by an expert center.

Additionally, advances in imaging techniques in magnetic resonance angiography (MRA) have been developed in CTEPH. Contrast-enhanced MRA can be used for morphological assessment of the pulmonary vasculature, and has been shown to demonstrate the typical features of chronic thromboembolic disease. However, the interpretation of these features solely by means of MRA has shown low sensitivity levels as compared to conventional pulmonary angiography.[37,38] Other potential uses of magnetic resonance imaging (MRI) include the structural and functional assessment of the heart, as it may provide information on end-systolic and diastolic volumes, ejection fraction, and muscle mass.[39] In this respect cardiac MRI has been used to study cardiac (dys)function in CTEPH patients, and it was used to demonstrate the restoration of RV remodelling and function after hemodynamically successful PTE (Figure 4).[40,41] In addition, 3D contrast-enhanced lung perfusion MRI may provide insight into regional pulmonary perfusion by tracking the dynamic passage of a contrast bolus. Although no comparison with the standard of reference was made, in a recent study in 68 patients with proven CTEPH, 3D contrast-enhanced lung perfusion MRI showed a sensitivity of 97% for the diagnosis of chronic thromboembolic disease, as compared to CT angiography (94%) and perfusion scanning (96%).[42] Despite these promising results, definitive data on direct comparison of MRA with conventional biplane angiography are still lacking.

Although studies using CT angiography and MRA may indicate that both modalities can be used to evaluate for presence of chronic thromboembolic disease and to obtain additional relevant information, currently both techniques still appear to underestimate the degree of the vascular obstruction.[2] In particular, the absence of reported radiographic abnormalities does not rule out surgically accessible chronic thromboembolic disease.[11] As noted before, in patients with proven chronic thromboembolic disease without evidence for PH at rest, consideration for pursuing additional investigations to evaluate exercise hemodynamics have been suggested to evaluate for presence of a possible exercise-induced compromised pulmonary circulation. However, this approach needs to be studied further.

PREOPERATIVE EVALUATION

In general, patients undergoing PTE typically exhibit a preoperative PVR >300 dynes·s·cm^{-5}, usually in the range of 800-1200 dynes·s·cm^{-5}, at rest or during exercise.[11,43] Currently, the

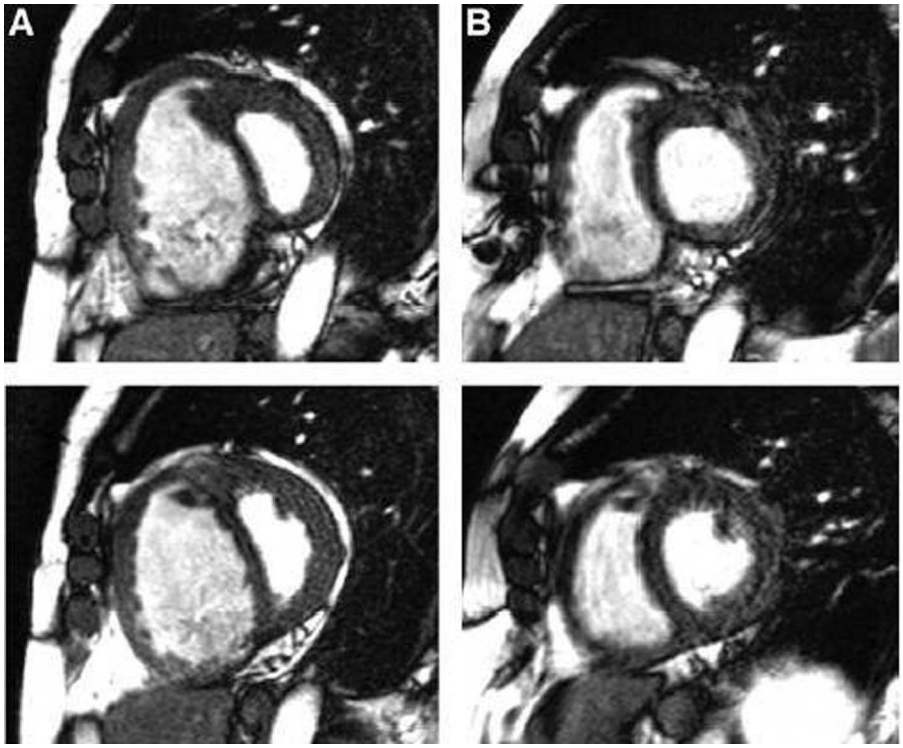

Figure 4: MRI short-axis cine images at basal (upper panel) and midventricular (lower panel) level, before (A) and after (B) PTE. Note the encroachment of the interventricular septum into the LV before PTE, and the normalization of the septal bowing after PTE. Note also the reversal of RV hypertrophy and the improvement in RV and LV volume.
Adapted from Reesink HJ, Marcus JT, Tulevski II, et al. Reverse right ventricular remodeling after pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension: utility of magnetic resonance imaging to demonstrate restoration of the right ventricle. *J Thorac Cardiovasc Surg.* 2007;133(1):58-64 with permission from Elsevier.

decision to perform a PTE in a distinct CTEPH patient is based on several objective and subjective factors that should be carefully defined during the preoperative evaluation.[11,13,44,45] Surgery can be considered if the pulmonary vascular obstruction results in hemodynamic and ventilatory impairment at rest or during exercise.[11]

Assessment of operability depends on surgically accessible lesions and therefore on the localization of the chronic thromboemboli. In general, proximal disease is confined to the main and/or lobar pulmonary arteries. Chronic thromboembolic occlusions of segmental and/or even subsegmental arteries are more difficult to treat surgically, but may be operable in highly experienced centers.[11,13,44,45] Secondly, prediction of postoperative outcome in terms of mortality, improvement in pulmonary hemodynamics after surgery, and the risk for a complicated postoperative course needs to be addressed. This is still in part subjective and highly dependent on CTEPH-specific expertise; it requires substantial experience to correlate the degree of hemodynamic perturbation, ie, mPAP and PVR, with the extent of the surgically accessible thromboembolic disease determined by pulmonary angiography.

In general, a preoperative PVR of more than 1000 dynes·s·cm^{-5} in the absence of substantial thromboembolic disease has been associated consistently with a high risk for persistent postoperative PH and increased mortality rates.[13,44,46] In these patients, the high preoperative PVR is likely to be in major part caused by a small-vessel arteriopathy in the nonobstructed vessels, which cannot be treated surgically. Therefore, it is of critical importance to identify patients at risk for significant small-vessel disease. However, at present, reliable and easily applicable diagnostic techniques to determine such patients are limited.[47] Moreover, the risk for postoperative persistent PH must be weighed against the chance to cure a patient with a progressive and potentially lethal disease.

For assessment of the relative contribution of a small vessel component to the PVR, the previously reported pulmonary artery occlusion technique represents a promising option. It is based on the assumption that the decaying pulmonary arterial occlusion pressure waveform can be used to estimate precapillary pressures; the PVR can then be partitioned into large arterial (upstream) and small arterial plus venous (downstream) components.[47,48] An inverse correlation has been demonstrated between the percent of upstream resistance and postoperative mPAP and PVR.[48] This technique, however, is technically highly challenging and still needs further clinical validation.[49] An alternative and simpler method to distinguish proximal from distal disease uses a particular feature of the Doppler-derived pulmonary flow profile. The midsystolic deceleration in pulmonary flow, the so-called pulmonary flow systolic notch, was shown to occur significantly later during the systole in patients with idiopathic PAH as compared to patients with proximal PE.[50] In a dog model, compared to constriction of proximal pulmonary arteries, experimentally induced microembolization of distal pulmonary arteries resulted in a later notch.[51] In CTEPH patients who underwent PTE, we showed that a late notch defined as a notch ratio >1 was indeed associated with a higher risk for persistent PH and an increased in-hospital mortality.[52]

In addition, risk for adverse outcome after PTE has been attributed to various comorbid factors, in particular the coexistence of chronic obstructive or restrictive lung disease.[11] Revascularization of lung areas with emphysema or interstitial lung disease may be associated with marked postoperative hypoxemia, thereby decreasing the PTE-associated hemodynamic benefits. Moreover, age, marked obesity, renal or hepatic insufficiency, and malignancy with a reasonable life expectancy should be taken into consideration, but none of these factors should pose an absolute contraindication for surgery.[53,54]

Although patients with proximal

CTEPH may benefit from medical treatment,[12,55-57] medical pretreatment prior to PTE is not indicated in the vast majority of patients. It is recommended that whenever possible PTE should be performed without any delay.[58] Furthermore, medical treatment may never be considered an alternative for PTE in patients with surgically accessible and thereby curable CTEPH. A full discussion regarding medical therapy for inoperable and recurrent PH in CTEPH is covered elsewhere in this issue.

CONCLUSION

In patients with PH or suspected to suffer from PH, diagnostic workup including V/Q scintigraphy should be performed to elucidate the underlying etiology. In case of an abnormal V/Q scan, pulmonary angiography and right heart catheterization are the gold standard for diagnosing CTEPH. PTE is the treatment of first choice, and for further evaluation of operability and preoperative risk patients should be referred to a CTEPH expert center.

References

1. Fedullo P, Kerr KM, Kim NH, Auger WR. Chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med.* 2011;183(12):1605-1613.
2. Hoeper MM, Mayer E, Simonneau G, Rubin LJ. Chronic thromboembolic pulmonary hypertension. *Circulation.* 2006;113(16):2011-2020.
3. Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC); European Respiratory Society (ERS); International Society of Heart and Lung Transplantation (ISHLT); Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J.* 2009;34(6):1219-1263.
4. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation.* 2011;124(18):1973-1981.
5. Bonderman D, Wilkens H, Wakounig S, et al. Risk factors for chronic thromboembolic pulmonary hypertension. *Eur Respir J.* 2009;33(2):325-331.
6. Bonderman D, Jakowitsch J, Adlbrecht C, et al. Medical conditions increasing the risk of chronic thromboembolic pulmonary hypertension. *Thromb Haemost.* 2005;93(3):512-516.
7. Auger WR, Permpikul P, Moser KM. Lupus anticoagulant, heparin use, and thrombocytopenia in patients with chronic thromboembolic pulmonary hypertension: a preliminary report. *Am J Med.* 1995;99(4):392-396.
8. Bonderman D, Turecek PL, Jakowitsch J, et al. High prevalence of elevated clotting factor VIII in chronic thromboembolic pulmonary hypertension. *Thromb Haemost.* 2003;90(3):372-376.
9. Lewczuk J, Piszko P, Jagas J, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. *Chest.* 2001;119(3):818-823.
10. Korkmaz A, Ozlu T, Ozsu S, Kazaz Z, Bulbul Y. Long-term outcomes in acute pulmonary thromboembolism: the incidence of chronic thromboembolic pulmonary hypertension and associated risk factors. *Clin Appl Thromb Hemost.* 2012;18(3):281-288.
11. Fedullo PF, Auger WR, Kerr KM, Rubin LJ. Chronic thromboembolic pulmonary hypertension. *N Engl J Med.* 2001;345(20):1465-1472.
12. Bresser P, Fedullo PF, Auger WR, et al. Continuous intravenous epoprostenol for chronic thromboembolic pulmonary hypertension. *Eur Respir J.* 2004;23(4):595-600.
13. Madani MM, Auger WR, Pretorius V, et al. Pulmonary endarterectomy: recent changes in a single institution's experience of more than 2,700 patients. *Ann Thorac Surg.* 2012;94(1):97-103.
14. Mayer E, Jenkins D, Lindner J, et al. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *J Thorac Cardiovasc Surg.* 2011;141(3):702-710.
15. Reesink HJ, van Delden OM, Kloek JJ, Jansen HM, Reekers JA, Bresser P. Embolization for hemoptysis in chronic thromboembolic pulmonary hypertension: report of two cases and a review of the literature. *Cardiovasc Intervent Radiol.* 2007;30(1):136-139.
16. Holverda S, Gan CT, Marcus JT, Postmus PE, Boonstra A, Vonk-Noordegraaf A. Impaired stroke volume response to exercise in pulmonary arterial hypertension. *J Am Coll Cardiol.* 2006;47(8):1732-1733.
17. Raeside DA, Smith A, Brown A, et al. Pulmonary artery pressure measurement during exercise testing in patients with suspected pulmonary hypertension. *Eur Respir J.* 2000;16(2):282-287.
18. Van der Plas MN, Reesink HJ, Roos CM, van Steenwijk RP, Kloek JJ, Bresser P. Pulmonary endarterectomy improves dyspnea by the relief of dead space ventilation. *Ann Thorac Surg.* 2010;89(2):347-352.
19. Woodruff WW 3rd, Hoeck BE, Chitwood WR Jr, Lyerly HK, Sabiston DC Jr, Chen JT. Radiographic findings in pulmonary hypertension from unresolved embolism. *AJR Am J Roentgenol.* 1985;144(4):681-686.
20. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest.* 2004;126(1 Suppl):14S–34S.
21. Yared K, Noseworthy P, Weyman AE, McCabe E, Picard MH, Baggish AL. Pulmonary artery acceleration time provides an accurate estimate of systolic pulmonary arterial pressure during transthoracic echocardiography. *J Am Soc Echocardiogr.* 2011;24(6):687-692.
22. Grünig E, Weissmann S, Ehlken N, et al. Stress Doppler echocardiography in relatives of patients with idiopathic and familial pulmonary arterial hypertension: results of a multicenter European analysis of pulmonary artery pressure response to exercise and hypoxia. *Circulation.* 2009;119(13):1747-1757.
23. Ryan KL, Fedullo PF, Davis GB, Vasquez TE, Moser KM. Perfusion scan findings understate the severity of angiographic and hemodynamic compromise in chronic thromboembolic pulmonary hypertension. *Chest.* 1988;93(6):1180-1185.
24. Thistlethwaite PA, Madani M, Jamieson SW. Pulmonary thromboendarterectomy surgery. *Cardiol Clin.* 2004;22(3):467-478, vii.
25. Auger WR, Fedullo PF. Chronic thromboembolic pulmonary hypertension. *Semin Respir Crit Care Med.* 2009;30(4):471-483.
26. Bailey CL, Channick RN, Auger WR, et al. "High probability" perfusion lung scans in pulmonary venoocclusive disease. *Am J Respir Crit Care Med.* 2000;162(5):1974-1978.
27. Rush C, Langleben D, Schlesinger RD, Stern J, Wang NS, Lamoureux E. Lung scintigraphy in pulmonary capillary hemangiomatosis. A rare disorder causing primary pulmonary hypertension. *Clin Nucl Med.* 1991;16(12):913-917.
28. Thistlethwaite PA, Auger WR, Madani MM, Pradhan S, Kapelanski DP, Jamieson SW. Pulmonary thromboendarterectomy combined with other cardiac operations: indications, surgical approach, and outcome. *Ann Thorac Surg.* 2001;72(1):13-17.
29. Rossi SE, McAdams HP, Rosado-de-Christenson ML, Franks TJ, Galvin JR. Fibrosing mediastinitis. *Radiographics.* 2001;21(3):737-757.
30. Shields JJ, Cho KJ, Geisinger KR. Pulmonary artery constriction by mediastinal lymphoma simulating pulmonary embolus. *AJR Am J Roentgenol.* 1980;135(1):147-150.
31. Castañer E, Gallardo X, Ballesteros E, et al. CT diagnosis of chronic pulmonary thromboembolism. *Radiographics.* 2009;29(1):31-50.
32. King MA, Bergin CJ, Yeung DW, et al. Chronic pulmonary thromboembolism: detection of regional hypoperfusion with CT. *Radiology.* 1994;191(2):359-363.
33. Kauczor HU, Schwickert HC, Mayer E, Schweden F, Schild HH, Thelen M. Spiral CT of bronchial arteries in chronic thromboembolism. *J Comput Assist Tomogr.* 1994;18(6):855-861.
34. Dournes G, Verdier D, Montaudon M, et al. Dual-energy CT perfusion and angiography in chronic thromboembolic pulmonary hypertension: diagnostic accuracy and concordance with radionuclide scintigraphy. *Eur Radiol.* 2014;24(1):42-51.
35. Sugiura T, Tanabe N, Matsuura Y, et al. Role of 320-slice CT imaging in the diagnostic workup of patients with chronic thromboembolic pulmonary hypertension. *Chest.* 2013;143(4):1070-1077.
36. Moser KM, Auger WR, Fedullo PF. Chronic major-vessel thromboembolic pulmonary hypertension. *Circulation.* 1990;81(6):1735-1743.
37. Kreitner KF, Ley S, Kauczor HU, et al. Chronic thromboembolic pulmonary hypertension: pre- and postoperative assessment with breath-hold MR imaging techniques. *Radiology.* 2004;232(2):535-543.
38. Nikolaou K, Schoenberg SO, Attenberger U,

et al. Pulmonary arterial hypertension: diagnosis with fast perfusion MR imaging and high-spatial-resolution MR angiography–preliminary experience. *Radiology.* 2005;236(2):694-703.
39. Alfakih K, Reid S, Jones T, Sivananthan M. Assessment of ventricular function and mass by cardiac magnetic resonance imaging. *Eur Radiol.* 2004;14(10):1813-1822.
40. Kreitner KF, Kunz RP, Ley S, et al. Chronic thromboembolic pulmonary hypertension - assessment by magnetic resonance imaging. *Eur Radiol.* 2007;17(1):11-21.
41. Reesink HJ, Marcus JT, Tulevski II, et al. Reverse right ventricular remodeling after pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension: utility of magnetic resonance imaging to demonstrate restoration of the right ventricle. *J Thorac Cardiovasc Surg.* 2007;133(1):58-64.
42. Rajaram S, Swift AJ, Telfer A, et al. 3D contrast-enhanced lung perfusion MRI is an effective screening tool for chronic thromboembolic pulmonary hypertension: results from the ASPIRE Registry. *Thorax.* 2013;68(7):677-678.
43. Thistlethwaite PA, Jamieson SW. Pulmonary thromboendarterectomy. *Ann Thorac Surg.* 2004; 78(2):746-747.
44. Dartevelle P, Fadel E, Mussot S, et al. Chronic thromboembolic pulmonary hypertension. *Eur Respir J.* 2004;23(4):637-648.
45. Jamieson SW, Kapelanski DP. Pulmonary endarterectomy. *Curr Probl Surg.* 2000;37(3): 165-252.
46. Hartz RS, Byrne JG, Levitsky S, Park J, Rich S. Predictors of mortality in pulmonary thromboendarterectomy. *Ann Thorac Surg.* 1996;62(5):1255-1259.
47. Kim NH. Assessment of operability in chronic thromboembolic pulmonary hypertension. *Proc Am Thorac Soc.* 2006;3(7):584-588.
48. Kim NH, Fesler P, Channick RN, et al. Preoperative partitioning of pulmonary vascular resistance correlates with early outcome after thromboendarterectomy for chronic thromboembolic pulmonary hypertension. *Circulation.* 2004; 109(1):18-22.
49. Toshner M, Suntharalingam J, Fesler P, et al. Occlusion pressure analysis role in partitioning of pulmonary vascular resistance in CTEPH. *Eur Respir J.* 2012;40(3):612-617.
50. Torbicki A, Kurzyna M, Ciurzynski M, et al. Proximal pulmonary emboli modify right ventricular ejection pattern. *Eur Respir J.* 1999;13(3): 616-621.
51. Furuno Y, Nagamoto Y, Fujita M, Kaku T, Sakurai S, Kuroiwa A. Reflection as a cause of mid-systolic deceleration of pulmonary flow wave in dogs with acute pulmonary hypertension: comparison of pulmonary artery constriction with pulmonary embolisation. *Cardiovasc Res.* 1991; 25(2):118-124.
52. Hardziyenka M, Reesink HJ, Bouma BJ, et al. A novel echocardiographic predictor of in-hospital mortality and mid-term haemodynamic improvement after pulmonary endarterectomy for chronic thrombo-embolic pulmonary hypertension. *Eur Heart J.* 2007;28(7):842-849.
53. Berman M, Hardman G, Sharples L, et al. Pulmonary endarterectomy: outcomes in patients aged >70. *Eur J Cardiothorac Surg.* 2012;41(6): e154–e160.
54. Kunihara T, Gerdts J, Groesdonk H, et al. Predictors of postoperative outcome after pulmonary endarterectomy from a 14-year experience with 279 patients. *Eur J Cardiothorac Surg.* 2011; 40(1):154-161.
55. Reesink HJ, Surie S, Kloek JJ, et al. Bosentan as a bridge to pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. *J Thorac Cardiovasc Surg.* 2010;139(1):85-91.
56. Surie S, Reesink HJ, Marcus JT, et al. Bosentan treatment is associated with improvement of right ventricular function and remodeling in chronic thromboembolic pulmonary hypertension. *Clin Cardiol.* 2013;36(11):698-703.
57. Nagaya N, Sasaki N, Ando M, et al. Prostacyclin therapy before pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension. *Chest.* 2003;123(2):338-343.
58. Jensen KW, Kerr KM, Fedullo PF, et al. Pulmonary hypertensive medical therapy in chronic thromboembolic pulmonary hypertension before pulmonary thromboendarterectomy. *Circulation.* 2009;120(13):1248-1254.