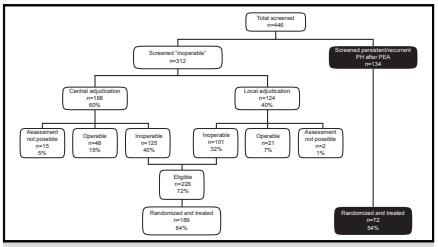
Operability assessment in CTEPH: Lessons from the CHEST-1 study

David P. Jenkins, BSc, MBBS, FRCS (CTh), MS,[a] Andrzej Biederman, MD,[b] Andrea M. D'Armini, MD,[c] Philippe G. Dartevelle, MD,[d] Hui-Li Gan, MD,[e] Walter Klepetko, MD,[f] Jaroslav Lindner, MD,[g] Eckhard Mayer, MD,[h] and Michael M. Madani, MD[i]

ABSTRACT

Pulmonary endarterectomy is the gold standard treatment for chronic thromboembolic pulmonary hypertension and is potentially curative, although some patients are unsuitable for pulmonary endarterectomy and require alternative management. Lack of standardized assessment of pulmonary endarterectomy eligibility risks suboptimal treatment in some patients. We discuss the implications for future clinical trials and practice of a unique operability assessment in patients who have chronic thromboembolic pulmonary hypertension and were initially screened for inclusion in the CHEST-1 (Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase Stimulator Trial-1) study. The CHEST-1 study evaluated riociguat for the treatment of inoperable chronic thromboembolic pulmonary hypertension (CTEPH) or persistent/recurrent pulmonary hypertension after pulmonary endarterectomy. Screened patients who were initially considered ''inoperable'' underwent central independent adjudication by a committee of experienced surgeons, or local adjudication in collaboration with an experienced surgeon. Operability decisions were based on accessibility of thrombi and the association between pulmonary vascular resistance (PVR) and the extent of obstruction, using pulmonary angiography/computed tomography with ventilation/perfusion scintigraphy as the minimum diagnostic tests. Of 446 patients screened for CHEST-1, a total of 188 and 124 underwent central and local adjudication, respectively, after being initially considered to be ''inoperable.'' After a second assessment by an experienced surgeon, 69 of these 312 ''inoperable'' patients were deemed operable. Rigorous measures in CHEST-1 guaranteed that only technically inoperable patients, or patients who had persistent/recurrent pulmonary hypertension, were enrolled, thus ensuring that only patients for whom surgery was not an option were enrolled. This study design sets new standards for future clinical trials and practice in CTEPH, helping to ensure that patients who have CTEPH receive optimal treatment. (J Thorac Cardiovasc Surg 2016;152:669-74)



Classification of surgical eligibility after operability assessment in the CHEST-1 study.

Central Message

The CHEST-1 operability assessment sets new standards for CTEPH trials, ensuring that patients who are eligible for pulmonary endarterectomy are correctly identified.

Perspective

Pulmonary endarterectomy is potentially curative in CTEPH. Some patients are ineligible for the surgery, but operability assessment is complex and subjective, and patients can be wrongly designated as inoperable. The operability assessment methodology presented here from the CHEST-1 study is designed to ensure that all patients who may benefit from pulmonary endarterectomy are correctly identified.

See Articles page 763 and 872.

See Editorial Commentaries page 675, 771, and 879.

See Editorial page 656.

From the [a]National Pulmonary Endarterectomy Service, Department of Cardiothoracic Surgery, Papworth Hospital, Cambridge, United Kingdom; [b]Department of Cardiac Surgery, Allenort Hospital, Warsaw, Poland; [c]Division of Cardiothoracic Surgery, Foundation ''I.R.C.C.S. Policlinico San Matteo,'' University of Pavia School of Medicine, Pavia, Italy; [d]Department of Thoracic and Vascular Surgery and Heart Lung Transplantation, Marie-Lannelongue Hospital, Paris-Sud University, Le Plessis-Robinson, France; [e]Department of Cardiac Surgery, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung, and Blood Vessel Disease, Beijing, China; [f]Department of Cardiothoracic Surgery, Vienna General Hospital, Medical University of Vienna, Vienna, Austria; [g]2nd Surgical Department—Clinical Department of Cardiovascular Surgery, First Faculty of Medicine and General Teaching Hospital, Charles University Prague, Prague, Czech Republic; [h]Kerckhoff Heart and Lung Center, Bad Nauheim, Germany; and [i]Division of Cardiovascular and Thoracic Surgery, University of California San Diego Medical Center, San Diego, Calif.

D.P.J., A.B., W.K., J.L., P.G.D., H.-L.G., and M.M.M. were members of the CHEST-1 operability assessment committee and contributed to the analysis and interpretation of data. A.M.D. was a CHEST-1 investigator directly involved in the recruitment and care of the participants, a member of the CHEST-1 operability assessment committee, and contributed to the analysis and interpretation of data; E.M. was a member of the steering committee for CHEST-1 and contributed to the analysis and interpretation of data. All authors contributed to the writing and revision of the article for intellectual content, and they have reviewed and approved the final version for submission.

Received for publication Dec 8, 2015; revisions received Feb 8, 2016; accepted for publication Feb 21, 2016; available ahead of print April 12, 2016.

Address for reprints: David P. Jenkins, BSc, MBBS, FRCS (CTh), MS, National Pulmonary Endarterectomy Service, Department of Cardiothoracic Surgery, Papworth Hospital, Cambridge, CB23 3RE, United Kingdom (E-mail: david.jenkins@papworth.nhs.uk).

0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2016.02.062

Abbreviations and Acronyms

CHEST-1 = Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Trial-1
CT = computed tomography
CTEPH = chronic thromboembolic pulmonary hypertension
PVR = pulmonary vascular resistance

Supplemental material is available online.

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by obstruction of the pulmonary vasculature by residual organized thrombi,[1,2] leading to increased pulmonary vascular resistance (PVR), progressive pulmonary hypertension, and right ventricular failure.[3-5] CTEPH is a major cause of severe pulmonary hypertension, yet the disease remains underdiagnosed.[6] Early diagnosis is essential to identify the most appropriate treatment, without which prognosis is poor.[6,7]

Pulmonary endarterectomy is the recommended treatment for CTEPH and is potentially curative.[8,9] However, patients who have distal disease may not benefit from pulmonary endarterectomy, and patients who have certain comorbidities are ineligible, whereas others have persistent/recurrent pulmonary hypertension after surgery.[6,8-10] For some of these patients, specifically those deemed technically inoperable owing to distal disease, and those who have persistent/recurrent pulmonary hypertension after pulmonary endarterectomy, medical therapy should be considered.

Appropriate assessment of operability is vital to ensure that patients receive the most suitable treatment, and that patients who have operable disease are not misclassified and denied pulmonary endarterectomy. However, the assessment of operability is subjective and challenging[8]; in the absence of a risk-stratification scoring system, making a consistent assessment is difficult, in both clinical practice and multicenter clinical trials in CTEPH. In view of this, all patients who have suspected CTEPH should be referred to an expert center for confirmation of diagnosis, assessment of operability, and treatment.[8,11,12]

Nonetheless, in patients with truly inoperable disease and those who have symptomatic residual/recurrent pulmonary hypertension after pulmonary endarterectomy, specific drug therapy for pulmonary hypertension may play a role. Previous randomized controlled studies of pulmonary arterial hypertension–targeted medications in patients who have CTEPH have shown variable clinical effectiveness.[13,14] Riociguat, a novel soluble guanylate cyclase stimulator[15-17] is approved for the treatment of inoperable or persistent/recurrent CTEPH, based on the pivotal phase III Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Trial-1 (CHEST-1) study.[18]

CHEST-1 was a multicenter, randomized, double-blind, placebo-controlled study; the primary endpoint was a change from baseline in 6-minute walking distance after 16 weeks of treatment. Rigorous adjudication in CHEST-1 guaranteed that only technically inoperable patients, and patients who had persistent/recurrent pulmonary hypertension, were enrolled. CHEST-1 was the first large randomized clinical trial of a pharmacotherapy in CTEPH to demonstrate statistically significant effectiveness, in terms of both increased 6-minute walking distance (+39 m) and reduced PVR (-226 dyn/s/cm^{-5}) in patients who had inoperable CTEPH or persistent/recurrent pulmonary hypertension after pulmonary endarterectomy.[18] Here, we report the impact of the unique methodology employed to assess operability in CHEST-1 and discuss its implications for future clinical trials and clinical practice.

CURRENT GUIDELINE RECOMMENDATIONS

Current CTEPH guidelines recommend that diagnosis of CTEPH be carried out in a stepwise process, starting with echocardiography to assess the right ventricle and ventilation/perfusion scintigraphy (Figure E1) to look for mismatched perfusion defects (with a normal ventilation/perfusion scan, excluding CTEPH as a diagnosis). Once CTEPH is diagnosed, operability assessment requires at least one more good-quality radiologic investigation to examine the anatomic pattern of the occlusive thromboembolic disease, preferably a catheter-based selective pulmonary angiography in 2 planes.[8] High-quality computed tomography or magnetic resonance angiography are potentially suitable investigations in experienced CTEPH centers. Recurrent disease is relatively rare if anticoagulation is well controlled. However, if patients experience recurrent breathlessness, the investigations need to be repeated.[8]

Despite sophisticated imaging techniques, the assessment of technical feasibility of pulmonary endarterectomy, as dictated by the angiographic pattern of obstruction, is subjective and depends on the experience of the surgeon.[8] Furthermore, the correlation between the extent of thromboembolic obstruction and the degree of pulmonary hypertension influences any risk–benefit analysis. Radiographic and hemodynamic evaluations must be performed in tandem to determine operability and estimate the relative risk from undergoing pulmonary