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Background—Chronic thromboembolic pulmonary hypertension (CTEPH) is often a sequel of venous thromboembolism with fatal natural history; however, many cases can be cured by pulmonary endarterectomy. The clinical characteristics and current management of patients enrolled in an international CTEPH registry was investigated.

Methods and Results—The international registry included 679 newly diagnosed (≤6 months) consecutive patients with CTEPH, from February 2007 until January 2009. Diagnosis was confirmed by right heart catheterization, ventilation-perfusion lung scintigraphy, computerized tomography, and/or pulmonary angiography. At diagnosis, a median of 14.1 months had passed since first symptoms; 427 patients (62.9%) were considered operable, 247 (36.4%) nonoperable, and 5 (0.7%) had no operability data; 386 patients (56.8%, ranging from 12.0%– 60.9% across countries) underwent surgery. Operable patients did not differ from nonoperable patients relative to symptoms, New York Heart Association class, and hemodynamics. A history of acute pulmonary embolism was reported for 74.8% of patients (77.5% operable, 70.0% nonoperable). Associated conditions included thrombophilic disorder in 31.9% (37.1% operable, 23.5% nonoperable) and splenectomy in 3.4% of patients (1.9% operable, 5.7% nonoperable). At the time of CTEPH diagnosis, 37.7% of patients initiated at least 1 pulmonary arterial hypertension–targeted therapy (28.3% operable, 53.8% nonoperable). Pulmonary endarterectomy was performed with a 4.7% documented mortality rate.

Conclusions—Despite similarities in clinical presentation, operable and nonoperable CTEPH patients may have distinct associated medical conditions. Operability rates vary considerably across countries, and a substantial number of patients (operable and nonoperable) receive off-label pulmonary arterial hypertension–targeted treatments. **(*Circulation*. 2011; 124:00-00.)**

Key Words: hypertension, pulmonary ■ endarterectomy ■ chronic disease

Chronic thromboembolic pulmonary hypertension (CTEPH) most often results from obstruction of the pulmonary vascular bed by nonresolving thromboemboli. Chronic thromboembolic pulmonary hypertension can arise in patients after acute or recurrent pulmonary emboli or deep venous thrombosis.[1,2] Increased pulmonary vascular resistance (PVR) subsequently leads to progressive pulmonary hypertension and right heart failure. In the nonoccluded areas, a pulmonary arteriopathy indistinguishable from that of pulmonary arterial hypertension (PAH) can develop and contribute to disease progression.[3] The incidence of CTEPH is not known, but recent studies suggest that 1% to 3.8% of

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patients develop the condition within 2 years of acute pulmonary embolism.[4,5] Without intervention, the prognosis of patients with CTEPH is poor and depends on the hemodynamic severity of pulmonary hypertension.[6,7]

Clinical Perspective on p ●●●

Progress in surgical and medical treatment over the past decade has considerably improved the outcome of CTEPH patients. The only potentially curative treatment is surgical removal of the obstructive material by pulmonary endarterectomy (PEA).[8] However, a substantial percentage of patients with CTEPH are not operable, and ≈10% to 15% of operated patients suffer from persistent pulmonary hypertension.[9] These patients may benefit from PAH-targeted therapies.[10–13] Previously, retrospective data have been collected from 4 European referral centers for CTEPH from Austria, Czech Republic, Germany, and Slovak Republic,[14] and a national CTEPH registry was established in the United Kingdom.[15] Here, we present short-term data from the first prospective, large-scale, international registry of patients with CTEPH including operable and nonoperable cases. We describe history and current diagnostic and treatment procedures of newly diagnosed CTEPH patients and potential associated conditions.

Methods

Study Design

This prospective registry was designed to include newly diagnosed (≤6 months) consecutive patients with CTEPH who did not receive PAH-targeted treatment before diagnosis from centers in Europe and Canada between February 2007 and January 2009. The registry protocol did not interfere with the management of patients by their physician. Formal ethics approvals were obtained when required by the country's regulatory agency. The observation period was from study inclusion until death/transplantation or data analysis cut off (December 2009). Long-term follow-up is on-going.

Inclusion Criteria

At all participating institutions, the diagnosis of CTEPH was established according to clinical guidelines valid at study initiation[16] and within 6 months of inclusion in the registry. To qualify for inclusion, patients had to be ≥18 years of age and pulmonary hypertension was to be confirmed by right heart catheterization[16] indicating a mean pulmonary artery pressure (mPAP) ≥25 mm Hg at rest or ≥30 mm Hg after exercise and a pulmonary capillary wedge pressure ≤15 Chronic thromboembolic pulmonary hypertension mm Hg (or >15 mm Hg if justified).

Chronic thromboembolic pulmonary hypertension was to be confirmed as the cause of pulmonary hypertension by abnormalities in ventilation/perfusion scan (at least 1 mismatched segmental perfusion defect), computed tomography (CT) scan, and/or in pulmonary angiography. Proximal lesions (webs, bands, and narrowed vessels) were identified by CT scan/pulmonary angiography. Before diagnosis, patients were required to have at least 3 months of anticoagulation therapy and no PAH-targeted treatment.

Data Collection

Data were obtained from assessments that are routinely performed for CTEPH patients in clinical practice including medical history, clinical signs and symptoms, diagnosis, and treatment procedures.

Surgery

The PEA procedure has been described previously.[8,17] Criteria for nonoperability included distal pulmonary artery obstructions, imbalance between increased PVR and amount of accessible occlusions suggesting microvascular disease, PVR >1500 dyn·s·cm^{-5}, age, and comorbidity. Persistent pulmonary hypertension after PEA was defined as mPAP >25 mm Hg by right heart catheterization or systolic pulmonary arterial pressure >40 mm Hg by echocardiography.

Statistical Analysis

Data were analyzed with the SAS software package version 9.2. Results are expressed as medians with first and third quartiles (Q1–Q3) or numbers and percentages of patients with the assessment. Operable and nonoperable patients were compared using the Wilcoxon rank-sum test for continuous variables and the Fisher exact test for categorical variables. The reported *P* values are to be interpreted in the exploratory sense.

Results

Study Population

Between February 2007 and January 2009, 679 consecutive patients with recently diagnosed (≤6 months) CTEPH were prospectively enrolled in 26 European centers and 1 Canadian center across 16 different countries. At the time of data cut-off, patients had been included for a minimum of 10 months; for 107 patients, follow-up in the registry was terminated because of death (n=62), transplantation (n=1), move to another center (n=35), loss of follow-up (n=4), patient's request (n=3), and other reasons (n=2). On the basis of the surgeon's assessment, 427 patients (63.3%) were considered operable and 247 (36.6%) nonoperable (5 patients missing data). Nonoperability was due to inaccessibility of the occlusions (n=118), imbalance between increased PVR and amount of accessible occlusions (n=25), PVR >1500 dyn·s·cm^{-5} (n=6), age (n=5), comorbidities (n=33), or other reason (n=56) (4 patients missing data). The patient population was divided per treatment intention into 2 groups: operable and nonoperable. At the time of data cut-off, 386 patients (56.8%) had undergone surgery (these operated patients have been described elsewhere[17]); 37 operable patients had refused the procedure and did not have surgery and 7 had died before surgery (the Figure).

The characteristics of the patient population at inclusion are summarized in Table 1. The median age was 63 years, and 50.1% were men. The operable group was younger (median: 61 years) and included more men (53.4%) than the nonoperable group.

Most patients consulted first a pulmonologist (35.1%) or a cardiologist (34.4%) (n=678). At the time of CTEPH diagnosis, a median of 14.1 months had passed since the first symptoms were observed (Q1–Q3: 7.5–32.8 months, n=637): 14.9 months for operable and 13.1 month for nonoperable patients (*P*=0.4051). The median time from last acute pulmonary embolism to CTEPH diagnosis was 12.5 months (Q1–Q3: 5.7–33.6 months, n=448): 12.0 months for operable and 13.9 months for nonoperable patients (*P*=0.3609). Most common presenting symptoms were: dyspnea (99.1%), edema (40.5%), fatigue (31.5%), chest pain (15.3%), or syncope (13.7%) (n=676). At diagnosis, the majority of patients were in NYHA functional class III or IV. Operable patients did not differ from nonoperable patients relative to symptoms and NYHA class, although their walking distance tended to be higher, which could also be

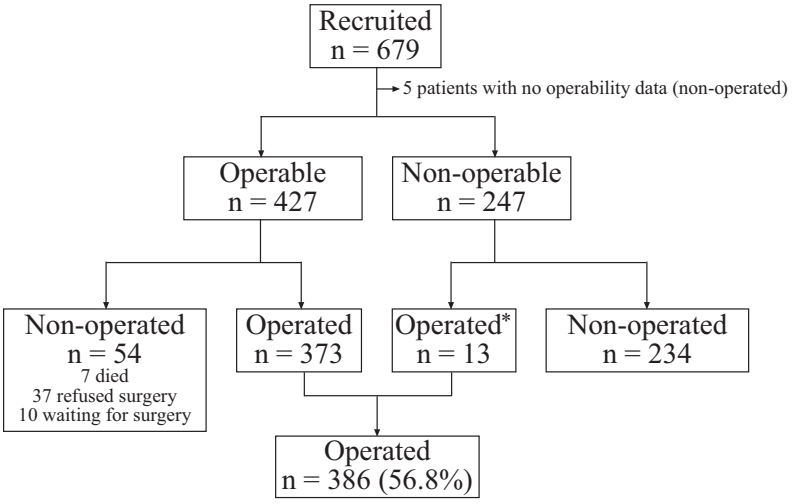

Figure. Patient disposition. Operable/nonoperable patients are assessed as such at diagnosis by the PEA surgeon according to predefined criteria (see Methods). Operated patients are those patients who effectively underwent surgery. *These patients initially deemed nonoperable were operated on.

associated with younger age (Table 1). Hematologic, biochemical and pulmonary function parameters were similar in both groups. Overall, blood group non-0 was more frequent (76.0% overall; 79.5% operable, 68.4% nonoperable patients, $P=0.0255$) than observed for the general population (45%–70% in Europe and Canada).

Previous pulmonary embolism was confirmed for 74.8% of all patients, and was more frequent and recurrent in the operable group of patients (Table 2). In this group, more patients had previous massive pulmonary embolism. Previous deep vein thrombosis was observed in 56.1% of patients and was also more common in the operable group of patients (Table 2). After an acute pulmonary embolism or deep vein thrombosis event, patients received anticoagulants, including oral anticoagulants (n=492/519), low molecular weight heparin (n=23), unfractionated heparin (n=3), and/or other (n=16). Thrombolytic treatment was initiated in 14.4% of patients and a vena cava filter or clip was placed in 12.4% of patients as prevention for recurrent pulmonary embolism. Operable patients had more frequently been treated with thrombolytics possibly because of the high incidence and severity of pulmonary embolism (Table 2).

An additional cause potentially contributing to pulmonary hypertension was documented in 20.9% of patients (Table 3). This percentage was lower for the operable group (17.1%) than for the nonoperable group (27.2%). In both groups, the most frequent associated condition was chronic obstructive pulmonary disease. The occurrence of medical conditions known previously to be associated with pulmonary embolism and CTEPH is listed in Table 4. A thrombophilic disorder and a family history of deep vein thrombosis or pulmonary embolism were more frequent in the operable group, whereas previous splenectomy, major surgery, congestive heart failure and a history of cancer were more frequent in the nonoperable group (Table 4). A history of cancer was reported for over 12% of the patients (10.1% operable and 16.6% nonoperable patients). Among 426 assessed patients, 118 (27.7%) had at least one established thrombotic risk factor including lupus anticoagulant/antiphospholipid antibodies (10.1%), protein S and C deficiency (9.6%; 8.9%), activated protein C resistance including Factor V Leiden mutation (7.7%), prothrombin gene mutation (3.5%), and antithrombin III deficiency (0.7%). At least one of these risk factors was documented in 30.5% of operable patients and in 22.3% of nonoperable patients ($P=0.0839$). In addition, Factor VIII was elevated in some patients (150% < Factor VIII <230% (n=19, 4.5%), or Factor VIII ≥230% (n=14, 3.3%)).

CTEPH Diagnosis

The diagnostic evaluations are presented in Table 5. Right heart catheterization data indicated clinically significant pulmonary hypertension with elevated PVR (median: 709 dyn ·

Table 1. Patients' Characteristics at Diagnosis

	All Patients (n=679)	Operable Patients* (n=427)	Nonoperable Patients* (n=247)	*P* (Exploratory)
Gender, % male	50.1	53.4	44.5	0.0308
Ethnicity, % white	95.9	95.3	96.7	0.4277
Age, y, median [Q1;Q3]	63 [51; 72]	61 [48; 70]	67 [57; 74]	<0.0001
Weight, kg, median [Q1;Q3]	75 [65; 87]	76 [66; 88]	73 [63; 82]	0.0161
NYHA class, % I/II/III/IV	0.7/17.8/68.6/12.8	0.5/19.2/67.7/12.6	1.2/15.8/70.4/12.6	0.4922
6MWD, m, median [Q1; Q3] (n)	329 [245; 427] (589)	340 [250; 435] (373)	315 [223; 400] (214)	0.0219
Blood group non-0, % (n)	76.0 (366)	79.5 (249)	68.4 (117)	0.0255

Values are expressed as medians with first and third quartiles (Q1; Q3) or percentages; (n): patients with assessment; *P* values from Wilcoxon rank-sum test or Fisher exact test. NYHA indicates new York Heart Association; 6MWD, 6-minute walking distance.

*Five patients had no data on operability.

Table 2. Patients' History of Venous Thromboembolism

	All Patients (n=679)	Operable Patients* (n=427)	Nonoperable Patients* (n=247)	*P* (Exploratory)
Confirmed previous acute PE, % (n)	74.8 (678)	77.5 (427)	70.0 (247)	0.0344
PE diagnosed more than once, % (n)	32.8 (469)	35.0 (303)	28.8 (163)	0.2145
Size of previous PE reported as massive, % (n)	40.8 (240)	47.1 (155)	29.4 (85)	0.0090
Confirmed previous DVT, % (n)	56.1 (426)	60.4 (280)	49.0 (143)	0.0295
Acute PE and DVT, % (n)	55.4 (413)	59.3 (270)	48.9 (141)	0.0477
Acute PE no DVT, % (n)	42.6 (413)	39.3 (270)	48.2 (141)	0.0926
Thrombolytic treatment, % (n)	14.4 (404)	18.5 (265)	6.6 (137)	0.0009
Vena cava filter implanted, % (n)	12.4 (491)	13.7 (322)	10.2 (166)	0.3139

P values from Fisher exact test. (n): patients with assessment. DVT indicates deep vein thrombosis; PE, pulmonary embolism.

*5 patients had no data on operability.

$s \cdot cm^{-5}$, mean: 782 dyn · s · cm^{-5}) and mPAP (median and mean: 47 mm Hg). In 69 patients, the pulmonary capillary wedge pressure was found to be >15 mm Hg. These patients were nevertheless included in the registry as in the presence of major vessel obstructions, the assessment of wedge pressure may be difficult, or sometimes impossible.[18]

Ventilation-perfusion lung scintigraphy showed abnormal perfusion scans in 98.7% of patients, whereas ventilation scans were abnormal in 19.0%. Pulmonary angiography demonstrated proximal lesions of the pulmonary artery in 63.0% of patients. Similar results were observed with CT pulmonary angiography, which indicated proximal lesions of the pulmonary artery in 60.4% of patients and also dilatation of bronchial arteries in 68.4% of patients. High resolution CT scan demonstrated mosaic perfusion pattern in 76.6% of patients. Proximal lesions and mosaic perfusion pattern were less common in the nonoperable patients.

Echocardiography revealed an enlarged right ventricle in 86.7% of patients (559/645) and abnormal right ventricular contractility in 66.7% (400/600).

Treatment at Diagnosis

At CTEPH diagnosis, 37.9% of the patients initiated at least one PAH-targeted therapy including phosphodiesterase type V inhibitor, endothelin receptor antagonist or prostacyclin analog (Table 6). The operable group received less PAH-targeted treatments than the nonoperable group (28.3% versus 53.8%; $P<0.0001$).

Surgery

Surgical management and risk factors for in-hospital and 1-year death have been presented elsewhere in detail.[17] Briefly, out of 384 assessed operated patients, 189 (49.2%) had a perioperative complication; 18 (4. 7%) patients died in hospital. After surgery, hemodynamics were markedly improved for patients with an assessment within 1 year after PEA: the median PVR decreased from 736 dyn · s · cm^{-5} before surgery to 248 dyn · s · cm^{-5} at the end of intensive care (Q1-Q3: 530–1010 and 180–398 dyn · s · cm^{-5}, respectively, n=252) and from 698 dyn · s · cm^{-5} before surgery to 235 dyn · s · cm^{-5} within 1 year after surgery (Q1–Q3: 501–989 and 178–320 dyn · s · cm^{-5}, respectively, n=70).

Per Country Analyses

The demography and management characteristics were collected for patients living in 16 countries, and, not surprisingly, differences were observed between individual countries. The median patient age in some countries could be as low as 55 years or as high as 68 years, and the percentage of men varied from 30.4% to 66.7%. Furthermore, the percentage of patients starting PAH-targeted treatment at diagnosis varied from 2.2% to 88.9%. The ranges for time from symptoms to diagnosis and to surgery were respectively 12 to 22 months and 12 to 116 days. A wide variation in nonoperability was observed between countries (from 12.0%–60.9%). Low-volume centers performing no or up to 10 PEAs per year (based on data from 2004–2006) reported a higher

Table 3. Other Reported Cause for PH at Diagnosis

	All Patients (n=679)	Operable Patients* (n=427)	Nonoperable Patients* (n=247)	*P* (Exploratory)
Other reported cause for PH, % (n)†	20.9 (675)	17.1 (427)	27.2 (246)	0.0022
COPD, %	9.5	8.4	11.0	0.2753
Sleep disorder breathing, %	3.1	2.1	4.9	0.0636
Left ventricular diastolic dysfunction, %	1.9	0.9	3.7	0.0188
Left-sided valvular heart disease, %	1.6	0.5	3.7	0.0027
Interstitial lung disease, %	1.3	0.7	2.4	0.0806
Drugs/toxins, %	1.5	1.2	2.0	0.5097

P values from the Fisher exact test. (n): patients with assessment. PH indicates pulmonary hypertension; COPD, chronic obstructive pulmonary disease.

*Five patients had no data on operability.

†Cause for PH is reported if occurrence is >1.5% in any patient group.

Table 4. Associated Medical Conditions at Diagnosis

	All Patients (n=679)	Operable Patients* (n=427)	Nonoperable Patients* (n=247)	*P* (Exploratory)
Associated conditions, % (n)	78.4 (677)	77.0 (426)	80.6 (247)	0.2878
Thrombophilic disorder, %	31.9	37.1	23.5	0.0003
Previous major surgery, %	21.7	18.8	26.7	0.0197
Varicose veins, %	20.8	20.4	21.1	0.8440
Obesity, %	17.6	16.7	19.0	0.4623
Chronic venous insufficiency, %	15.5	16.0	14.6	0.6596
Prolonged hospitalization, %	16.0	16.0	15.8	1.0000
History of cancer, %	12.7	10.1	16.6	0.0156
Coronary disease and/or myocardial infarction, %	11.8	11.0	13.4	0.3883
Thyroid disorder and hormone replacement therapy, %	8.4	7.7	9.3	0.4732
Family history of DVT or PE, %	6.6	8.2	4.0	0.0382
Fracture, %	5.5	5.9	4.5	0.4815
Non–insulin-dependent diabetes mellitus, %	5.2	5.4	4.9	0.8580
Congestive heart failure, %	4.6	2.8	7.7	0.0065
Splenectomy, %	3.4	1.9	5.7	0.0118
Ventriculoatrial shunt, %	0.9	0.7	1.2	0.6743
Inflammatory bowel disease, %	0.7	1.2	0	0.1641
Infection of ventriculoatrial shunt or pacemaker, %	0	0	0	…

P values from Fisher exact test. (n): patients with assessment. DVT indicates deep vein thrombosis; PE, pulmonary embolism.
*Five patients had no data on operability.

percentage of nonoperable patients (47.1% out of n=172) than intermediate centers performing 11 to 50 PEAs per year (31.5%, n=295) or high-volume centers performing >50 PEAs per year (34.4%, n=212) (P=0.0008), suggesting that center expertise may have influenced the decision to operate. However, further investigation would be necessary to ascertain the reasons for the variability observed in operability rates because a referral bias may also have affected the largest surgical centers.

Death/Transplantation

At the end of the observation period, 1 patient was documented as transplanted and 62 as dead. Most frequent causes for death were perioperative complications (n=18) and right

Table 5. Diagnosis Evaluations

	All Patients (n=679)	Operable Patients* (n=427)	Nonoperable Patients* (n=247)	*P* (Exploratory)
Right heart catheterization				
mPAP†, mm Hg, median [Q1; Q3] (n)	47 [38; 55] (669)	47 [38; 55] (423)	47 [38; 55] (244)	0.5064
PVR‡, dyn · s · cm^{-5}, median [Q1; Q3] (n)	709 [480; 988] (604)	717 [495; 963] (381)	691 [426; 1051] (221)	0.7408
Cardiac index, L · min^{-1} · m^{-2} median [Q1;Q3] (n)	2.2 [1.8; 2.7] (632)	2.2 [1.8; 2.7] (404)	2.3 [1.8; 2.8] (227)	0.1343
Scintigraphy, % (n)				
Perfusion scan abnormal	98.7 (535)	99.4 (344)	97.4 (189)	0.1031
Ventilation scan abnormal	19.0 (484)	17.5 (314)	22.0 (168)	0.2736
Angiography, % (n)				
Proximal lesions	63.0 (552)	70.9 (358)	48.2 (191)	<0.0001
CT scan, % (n)				
Proximal lesions	60.4 (541)	70.1 (345)	43.0 (193)	<0.0001
Dilation of bronchial arteries	68.4 (345)	75.0 (216)	57.0 (128)	0.0008
Mosaic perfusion pattern	76.6 (414)	82.4 (261)	67.1 (152)	0.0007

P values from Wilcoxon rank-sum test or Fisher exact test. (n): patients with assessment. CT indicates computed tomography; mPAP, mean pulmonary arterial pressure; and PVR, pulmonary vascular resistance.
*Five patients had no data on operability.
†mPAP: 12 values <25 mm Hg; 4 values >75 mm Hg.
‡PVR: 13 values <200 dyn · s · cm^{-5}.

Table 6. PAH-Targeted Therapy Initiated at Diagnosis

	All Patients (n=679)	Operable Patients* (n=427)	Nonoperable Patients* (n=247)	*P* (Exploratory)
PAH-targeted therapy, % (n)	37.9 (676)	28.3 (427)	53.8 (247)	<0.0001
Phosphodiesterase type V inhibitor, %	17.5	16.2	19.4	0.2923
Endothelin receptor antagonist, %	21.7	12.2	37.7	<0.0001
Prostacyclin analogue, %	2.7	1.6	4.5	0.0443
Combination therapies, %	4.0	1.6	7.7	0.0002

P values from Fisher exact test. (n): patients with assessment. PAH indicates pulmonary arterial hypertension.
*Five patients had no data on operability.

heart failure (n=17). Comparison between the operable and nonoperable patient groups will be performed once 3-year follow-up data are available.

Discussion

With 679 patients included from Europe and Canada, the present prospective registry represents the largest contemporary population of patients with CTEPH, including newly diagnosed operable and nonoperable cases. The aim of the current report is to describe the disease at presentation along with short-term outcome; long-term follow-up is currently ongoing. The main findings are differences in occurrence of associated medical conditions between operable and nonoperable patients despite similarities in disease presentation, suggesting that these patients represent 2 distinct subpopulations.

Although PEA is the acknowledged treatment of choice for CTEPH, between 10% and 50% of referred patients may not be eligible for this procedure.[19] In the current registry, 36.6% of the evaluated patients (n=674) were assessed as nonoperable, with a large variation between countries (from 12.0% to 60.9%). Criteria for surgical suitability have been described,[20] but remain expertise dependent and ill-defined as there is currently no consensus among experts about the definition of proximal CTEPH, potentially curable with surgery, and distal CTEPH, presumably associated with small vessel arteriopathy and poor surgical outcome.[21]

The registry results support the thromboembolic cause of CTEPH, with 74.8% of patients presenting with previous acute pulmonary embolism and 56.1% with previous deep vein thrombosis. This is in agreement with recent studies,[14,18] but contrasts with previous retrospective reports indicating no history of venous thromboembolism in 40% to 60% of the patients.[22–24] Increased awareness of thromboembolism in the participating registry centers may have contributed to higher detection. As previously documented,[18] a history of acute pulmonary embolism was less common in patients with a nonoperable disease. These patients also had less massive pulmonary embolism, which is in line with a more distal disease and a possible process of in situ thrombosis.[25] In this registry, 12.4% of patients received a vena cava filter as a treatment for recurrent acute pulmonary embolism and, as previously reported,[17] only 40.2% of operable patients had a vena cava filter inserted, whereas this preoperative procedure has been systematically applied in other patient series.[8,26]

Although CTEPH patients are a heterogeneous group with respect to hemodynamic status and surgical accessibility of pulmonary thromboemboli resulting in operability or nonoperability, they presented also with many similarities at diagnosis, suggesting an underlying common disease process. In line with previous reports,[8,14,15] CTEPH was almost equally frequent in men and women in their sixth decade of life. Operable patients were younger than nonoperable patients but presented with similar disease severity as assessed by New York Heart Association (NYHA) functional class. This is consistent with findings from Bonderman et al,[27] in a retrospective analysis of 181 European CTEPH patients, and from Condliffe et al[15] in a retrospective study of 469 CTEPH patients from the United Kingdom. An increased awareness of pulmonary embolism and of CTEPH as a subsequent complication may be responsible for reduced time to diagnosis in both operable and nonoperable patients after the last acute pulmonary embolism event (12.5 months) and the symptom onset (14.1 months) compared with past studies reporting a diagnostic delay of several years.[28,29] The symptoms preceding the diagnosis of CTEPH have been described previously,[1] and did not differ in the present study. Effective imaging technologies including conventional and CT pulmonary angiography were widely used to examine large-vessel occlusion, revealing a higher occurrence of proximal lesions in the group of patients that was operable.

Chronic thromboembolic pulmonary hypertension patients are characterized by numerous severe comorbidities.[14,18,30] In particular, chronic obstructive pulmonary disease was observed in as many as 9.5% of the patients. A history of splenectomy was more frequent in the CTEPH registry patients than reported in patients with other chronic pulmonary conditions,[30] and was frequently associated with nonoperability (ie, with a distal type of CTEPH or a significant comorbidity). This is in line with the postulated link between abnormal postsplenectomy erythrocyte activities or abnormal platelet activation and the development of a primarily distal CTEPH disease.[14,30] A history of cancer was reported in this registry for >12% of the patients, which supports the concept that malignancy and/or treatment for malignancy could be a risk factor for CTEPH.[14] A thrombophilic disorder was present in nearly one third of the patients, and as reported previously, CTEPH patients were more likely to have a blood group other than 0[14]; these observations were even more pronounced in the operable group. A number of inherited and acquired coagulation abnormalities have been identified in recent years that may contribute to the development of CTEPH. These include lupus anticoagulant and antiphospholipid antibodies; deficiencies of protein C, protein S, and antithrombin III; presence of factor V Leiden, and prothrom-

bin gene mutations.[23,31,32] These abnormalities were identified in 27.7% of the registry patients and tended overall to be more frequent in operable patients in line with more impaired thromboemboli resolution. The current results confirm that antiphospholipid antibodies, along with lupus anticoagulant, 2 thrombophilic factors associated with recurrent thrombosis,[33,34] are elevated in patients with CTEPH. However, a prothrombotic pathogenic mechanism involving Factor VIII in the development of CTEPH was not corroborated.[35] A detailed investigation of the risk factors involved in CTEPH will be the subject of a separate publication.

This registry emphasizes the seriousness of the disease, with 62 patients out of 679 documented as having died during the observation period of the study (≥10 months). It also reflects the changes that have occurred in the management of CTEPH over recent years, including the increasing success rate of PEA surgery and the availability of PAH-targeted therapies. The low in-hospital mortality rate of 4.7% after surgery reported here is in line with continuously improving surgical results in recent worldwide series.[8,15,27,36] Although surgical intervention with PEA is the preferred treatment in eligible patients, CTEPH patients may benefit from the pharmacotherapy that has been developed for PAH.[10,13] Despite the absence of robust data from randomized, controlled trials, the prescription of these medications, even in operable CTEPH, has increased over the past years.[15,37] Jensen et al[37] reported an increase in patients treated with PAH-targeted therapies before PEA from 19.9% in 2005 to 37% in 2007. This change in prescribing practice is confirmed by the present registry, with 28.3% of the operable patients and 53.8% of the nonoperable patients initiating at least 1 PAH-targeted therapy at diagnosis. Because of unequal medical resources and/or possibly different medical practices, these percentages can be highly country dependent. Cautious use of PAH-targeted therapies is, however, endorsed by current guidelines[38]: Preoperative treatment has been reported to have minimal effect on pre-PEA hemodynamics and no effect on post-PEA outcome,[37] and may induce unnecessary delay to a potentially curative surgical intervention.[17]

The limitations of the study are inherent to a registry design: Some assessments were not systematically collected, leading to underreporting (eg, blood groups and thrombotic risk factors). Given that most of the participating centers were referral centers for CTEPH and PEA, the proportion of operable patients may have been overestimated because of referral bias. Per country analyses have to be interpreted cautiously, because the number of patients in some countries could be small and not representative. Finally, no patient was excluded from the analysis even when not satisfying the inclusion criteria; as a consequence, 10 patients had no right heart catheterization.

Conclusions

The similarities between operable and nonoperable CTEPH patients necessitate a very careful diagnostic process with high-quality angiography and right heart catheterization hemodynamic evaluation to assess operability. Nevertheless, operable and nonoperable CTEPH patients may differ relative to the occurrence of associated medical conditions: In particular, thrombophilic disorders tend to be more frequent in operable patients, whereas splenectomy and cancer are more common in nonoperable patients. The registry data highlight the importance of previous venous thromboembolism events as a causal factor for the development of CTEPH, along with a significant role for associated medical risk factors as coexisting mechanisms in the disease process. A substantial number of patients (operable and nonoperable) are currently being treated with off-label treatments. The registry data also indicate that, whereas PEA can be performed with a low in-hospital mortality rate, operability rates may vary considerably across centers and countries. The indication for PEA is not clearly defined, and is dependent on the experience of the surgical team. With surgical progress constantly extending the selection of patients who can benefit from surgery, a consensus among experts is needed to reassess the criteria for operability. The ongoing 3-year follow-up of this large patient cohort will make it possible to evaluate the impact of the contemporary management of CTEPH on patient survival compared with published series.

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CLINICAL PERSPECTIVE

We present short-term data from a large, prospective, international (mostly European) noninterventional registry of newly diagnosed patients with chronic thromboembolic pulmonary hypertension, including operable and nonoperable cases. In this registry, the diagnosis of chronic thromboembolic pulmonary hypertension was often delayed, with a median of 14 months after the initial symptoms. Three quarters of patients had a history of prior acute pulmonary embolism. One third of patients received pulmonary endarterectomy with a mortality rate of 4.7%. Although clinical symptoms, New York Heart Association class, and hemodynamics were not different between operable and nonoperable patients, nonoperable patients were older, had a lower 6-minute walk test, had smaller pulmonary emboli in the past, were less likely to receive thrombolytic therapy with their prior pulmonary embolus, and were more likely to have other causes of pulmonary hypertension. The large difference in rates of pulmonary endarterectomy between countries suggests other local factors influenced the decision to operate on patients with chronic thromboembolic pulmonary hypertension. The indication for pulmonary endarterectomy is not clearly defined, and is dependent on the experience of the surgical team. About one third of patients (operable and nonoperable) received off-label pulmonary hypertension–targeted treatments. Finally, these data emphasize the deadly nature of the disease, with death documented for 62 patients out of 679 during the observation period of the study (≥10 months).