Update on Chronic Thromboembolic Pulmonary Hypertension, a Frequently Undiagnosed Condition

Irene M. Lang[a] and Walter Klepetko[b]

[a]Department of Internal Medicine II, Division of Cardiology, Vienna General Hospital, Medical University of Vienna, Austria
[b]Department of Surgery, Division of Cardiothoracic Surgery, Vienna General Hospital, Medical University of Vienna, Austria

Chronic thromboembolic pulmonary hypertension (CTEPH) results from an obstruction of the pulmonary vessels with organized blood clots. It is a common variant of pulmonary hypertension.[1] There are about 2500 new cases in the United States each year,[2] or a calculated prevalence of about 3 cases of CTEPH out of 100 cases of pulmonary embolism (approximately 20 per million). It is a long-term complication of symptomatic pulmonary embolism, with a cumulative incidence of 1% to 5% within 2 years after the embolic event.[2-5] In addition, about 40% of the cases of CTEPH originate from asymptomatic venous thromboembolism.[1,6]

Pathogenesis and Prognosis

The pathogenesis of CTEPH is unclear.[1] Although CTEPH is considered a venous thromboembolic (VTE) disorder, no classical thromboembolic risk factors measurable in plasma have been identified. By contrast, some, but not all risk factors of recurrent VTE, such as elevated factor VIII[7] and lupus anticoagulant/antiphospholipid antibodies, are present.[8] Male gender is not generally a risk factor for CTEPH; in fact, in Japan, female gender predominates.[9] In addition, no genetic basis for CTEPH has been detected. In contrast to pulmonary arterial hypertension (PAH) involving vessels smaller than 300 μm, CTEPH mainly affects large vessels[10] and is therefore amenable to surgical treatment.[11] Figure shows a typical surgical preparation, representing a cast of the pulmonary vascular bed, consisting of endothelium, smooth muscle cells, fibroblasts, and a fresh thrombus.

The type of CTEPH has been implicated in the surgical outcome[12] as follows: type I, presence of a central thrombus (surgical mortality, 2.1%); type II, thickened intima, fibrous webs, and bands within the lobar arteries (surgical mortality, 5.3%); type III, occlusions in the segmental and subsegmental branches (surgical mortality, 5%); or type IV, very distal thrombi (surgical mortality, 25%).

Jamieson et al reported a female predominance in type III disease.[13] In Japan, more females than males are affected, and the disease is associated with HLA-B*5201 and HLA-DPB1*0202.[14] Recent data expand these observations and demonstrate that female Japanese CTEPH patients were elderly, had a lower incidence of deep vein thrombosis, fewer acute embolic episodes, better cardiac function, lower arterial oxygen tension, and more peripheral thrombi, and showed less improvement following surgery than men.

Chronic thromboembolic pulmonary hypertension is a complex disorder that comprises a poorly understood major vessel vascular remodeling process as a consequence of symptomatic and asymptomatic pulmonary embolism, and a classical pulmonary arteriopathy[1,15] affecting arterioles and precapillary vessels <200 μm in diameter. Recent data suggest that the incidence of small vessel disease may be greater in patients with associated medical conditions,[16] eg, ventriculo-atrial shunts for the treatment of hydrocephalus, splenectomy, inflammatory bowel disease, low-grade malignancy, and thyroid replacement therapy. Based on recent insights, the mechanistic view of CTEPH as a disease caused by obliteration of the central pulmonary arteries due to a classical thrombotic process may have been too simplistic.[17] We speculate that pulmonary embolism may be followed by a pulmonary vascular remodeling process that is modified by infection,[18] immune

Correspondence: Dr I. Lang,
Professor of Vascular Biology, Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna,
Währinger Gürtel 18-20, 1090 Vienna, Austria
E-mail: irene.lang@meduniwien.ac.at

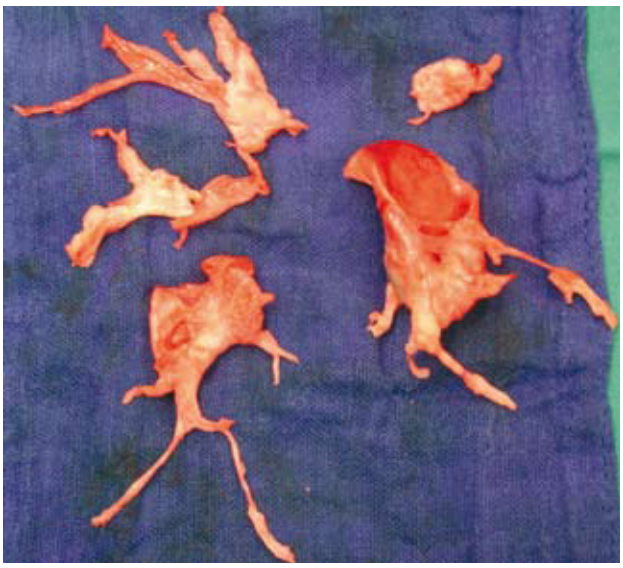

Figure. Typical pulmonary endarterectomy outcome as seen in 40% of the patients. The image shows the surgical specimen corresponding to a cast of the pulmonary arterial tree. The specimen is an example of type II disease.

phenomena,[8] thyroid hormone replacement, and malignancy.

Right heart failure and death are consequences of CTEPH if patients are not treated.[19] Hemodynamic variables have been identified as predictors of prognosis.[20,21] During the last few decades, pulmonary endarterectomy (PEA) has been considered the treatment of choice, with a perioperative mortality of only 4% to 10%, an excellent quality of life and, in certain cases, normalization of exercise capacity and, frequently, a normalization of resting hemodynamic parameters.[6] However, according to current data from large centers in which PEA is performed, a significant proportion of patients is not suitable for PEA or experiences no improvement or the recurrence of pulmonary hypertension.[22] Concomitant small vessel disease is a predictor of prognosis, whether or not the patient undergoes PEA,[16] and, theoretically, represents a therapeutic target for classical PAH drug therapy.[17]

Associated Factors

Splenectomy, ventriculo-atrial shunt, inflammatory bowel disease, and chronic osteomyelitis are associated with a higher incidence and a worse prognosis of CTEPH.[16] In a recent retrospective database study involving 3 European centers in which PEA is performed, data from 687 CTEPH patients at the time of diagnosis between 1996 and 2007 were compared with cohorts at the participating institutions with non-thromboembolic precapillary PAH. Ventriculo-atrial shunts and infected pacemakers (odds ratio [OR], 76.40; 95% confidence interval [CI], 7.67-10 351; *P*<.001), splenectomy (OR, 17.87; 95% CI, 1.56-2438; *P*=.017), previous VTE (OR, 4.52; 95% CI, 2.35-9.12; *P*<.001), recurrent VTE (OR, 14.49; 95% CI, 5.40-43.08; *P*<.001), non-O blood groups (OR, 2.09; 95% CI, 1.12-3.94; *P*=.019), and lupus anticoagulant/anti-phospholipid antibodies (OR, 4.20; 95% CI, 1.56-12.21; *P*=.004) were more frequently associated with CTEPH. Thyroid replacement therapy (OR, 6.10; 95% CI, 2.73-15.05; *P*<.001) and a history of malignancy (OR, 3.76; *P*=.005) emerged as novel risk factors for CTEPH. Taken together, the results of the study of this European database confirmed previous knowledge of the risk factors for CTEPH and identified thyroid replacement therapy and a history of malignancy as new medical conditions associated with CTEPH. Treatment with levothyroxine increases von Willebrand factor levels and shortens in vitro platelet plug formation, measured as collagen-epinephrine-induced closure time, thus possibly increasing thrombogenicity.[23]

Another multicenter, prospective, incident case registry has recently failed to confirm the negative impact of splenectomy alone on outcomes, regardless of the operability of the patient[24]; yet, only 6.7% of the patients had undergone previous splenectomy, and other associated conditions were not included in the analysis. One- and 3-year survival from the time of diagnosis was 82% and 70% for patients with nonsurgical disease and 88% and 76% for those treated surgically (*P*=.023). Initial functional improvement in patients with nonsurgical disease was noted but did not persist at 2 years. Significant functional and hemodynamic improvements were seen in surgically treated patients, with an increase in 6-minute walk distance of 105 meters (P<.001) at 3 months.[24] The data illustrate the importance of identifying patients with this increasingly treatable condition.

A prospective European multicenter CTEPH registry is underway and will elucidate the incidence, diagnosis, treatments and outcomes of contemporary CTEPH patients in Europe.[25]

Diagnosis

Symptoms of CTEPH are intermittent and occur once more than 60% of the pulmonary vasculature is compromised. Exercise intolerance and dyspnea are common symptoms, together with fatigue, chest pain, recurrent syncope induced by exercise and coughing, hemoptysis and vertigo. The course

of CTEPH is episodic, with long "honeymoon periods" of only mild or no symptoms.[10] Overall, the course is less insidious than that of PAH.[19]

The alveolar-arterial oxygen difference is increased at an early stage of the disease; subsequently, the partial pressure of oxygen is decreased and the partial pressure of carbon dioxide is increased.

At least one major segmental defect in the ventilation/perfusion (V/Q) scan leads to diagnosis. The performance of ventilation scintigraphy is not required if the chest radiograph is grossly normal.

Transthoracic echocardiography (TTE) is an important diagnostic tool, and serves as a screening method. Spiral computed tomography using intravenous contrast is a very accurate and important diagnostic tool. In addition to vascular diseases, the condition of the lung parenchyma can be evaluated.

Measurement of pulmonary artery resistance, cardiac index, and mean atrial pressure are required to assess the severity of the disease, operability, and prognosis.

Pulmonary Angiography

Prior to surgical intervention, pulmonary angiography must be performed. Only in very experienced centers with access to latest generation multislice computed tomography (CT) scanners can a diagnosis be attempted without a pulmonary angiogram. Vascular recesses, ligaments, increments, sudden changes in the vessel size and vascular occlusion are typical angiographic findings.[26] Abrupt changes in pulmonary vessel size, with bands, webs, pouches, and dilated central vessels with irregular tapering of the peripheral vasculature and segmental complete vessel obstruction are characteristic features of CTEPH.

Operability

Pulmonary endarterectomy is a realistic option for cure.[12] The assessment of operability of CTEPH is clearly center-specific and is subject to wide center-to-center variations.

A number of criteria have to be considered:

1. Symptomatic pulmonary hypertension with an invasively measured mean pulmonary arterial pressure (mPAP) of more than 25 mm Hg.

2. Diagnostic evaluation after at least 3 months of effective oral anticoagulation.

3. Evidence of surgically accessible thrombi according to pulmonary angiography and/or latest generation CT scanning, or complete unilateral occlusion of a main pulmonary artery.

4. A pulmonary vascular resistance ratio (<1200 dynes×cm×s^{-5}) and anticipated thrombus mass that makes a reduction of pulmonary vascular resistance (PVR) by more than 50% plausible after PEA.

5. A preoperative risk profile that does not rule out surgery:

– PVR <1000 dynes×cm×s^{-5}
– Absence of severe comorbidities
– Sufficient functional lung parenchyma
– High upstream resistance[27] (experimental)
– No associated medical conditions[28]
– Decrease in mPAP of at least 10% after administration of inhaled nitric oxide during diagnostic right heart catheterization[29]
– Favorable biomarker profile (heart-type free fatty acid binding protein <3 ng/mL,[30] asymmetric dimethyl-arginine <0.6 μmol/L[31])
– Patient informed consent
– Absence of isolated unilateral disease
– Male gender if the patient is Japanese[9]
– Notch ratio <1 (time interval from the onset of pulmonary artery systolic flow to the maximal systolic flow deceleration [t_1] divided by the time interval from the maximal systolic flow deceleration to the end of pulmonary artery systolic flow [t_2])[32]

Surgical Techniques and Outcomes

Cardiopulmonary function in patients with CTEPH can be normalized by pulmonary endarterectomy. The procedure involves the removal of organized and incorporated fibrous obstructive tissue from the pulmonary arteries during circulatory arrest under deep hypothermia. Mortality rates reported for patients who have undergone pulmonary endarterectomy range from 4% to 24%, and depend on the anatomic location of the most proximal thrombus. The operation is not an embolectomy but a true endarterectomy. Following incision in the proximal intrapericardial pulmonary artery, the correct endarterectomy plane is established and circumferentially followed down to the lobar, segmental, and subsegmental pulmonary artery branches in each lobe. The endarterectomy procedure in one lung can usually be completed within a 20-minute period of circulatory arrest. This is followed by reperfusion and another period of circulatory arrest for the endarterectomy on the contralateral side. With shorter cardiac arrest periods and the use of a cooling jacket for the head, cerebral compromise has been minimized. Perioperative morbidity is determined mainly by reperfusion edema, pneumonia and bleeding.[12] About 10% of the patients undergo some other

cardiovascular surgery simultaneously.[12] Both the natural history of the disease[20,21] and the surgical results are highly dependent on hemodynamics. A preoperative pulmonary vascular resistance above 1000 dynes×cm×s^{-5} increases operative risk. A postoperative pulmonary vascular resistance of over 500 dynes×cm×s^{-5} is a predictor of a poor long-term prognosis.[20]

Medical Treatment

Untreated, CTEPH has a poor prognosis, with over half of the patients with a mPAP greater than 50 mm Hg not surviving beyond one year after diagnosis.[20] Pulmonary hemodynamics and PVR are believed to be critical, because a significant reduction following surgery is associated with increased survival, and high preoperative values carry a significant risk of surgical mortality.[13] Despite the advances achieved with PEA, up to 50% of the patients are judged inoperable, and about 24% experience persistent or recurrent pulmonary hypertension after PEA.[22]

Histopathological studies of vascular changes in CTEPH have identified vascular lesions similar to those seen in idiopathic PAH.[33] These data have provided the rationale for considering pharmacological treatment of CTEPH.

Currently, the following indications for medical treatment of CTEPH appear justified:

– Inoperable distal disease
– Comorbidities considered to involve high-risk for surgery
– Bridge to PEA or transplantation for high-risk patients
– Persistent or residual pulmonary hypertension following PEA

The only study employing PAH medications in CTEPH that had significant statistical power to detect a statistical difference between study subjects and controls was the BENEFIT trial. Its rationale was well founded. Apart from several uncontrolled trials in CTEPH that suggested that bosentan was effective in improving exercise capacity and hemodynamics[34-36] in these patients, endothelin (ET)-mediated vascular remodeling was demonstrated in animal models of CTEPH,[37] and increased ET levels and ET_B receptor expression have been observed in CTEPH patients.[38]

Patients with either inoperable CTEPH or persistent/recurrent pulmonary hypertension after PEA (more than 6 months after PEA) were included. Independent co-primary endpoints were a change in PVR as a percentage of baseline and a change from baseline in six-minute walk distance after 16 weeks of treatment with bosentan or placebo. Secondary endpoints included change from baseline in World Health Organization functional class and other hemodynamic parameters. One hundred fifty-seven patients were enrolled and randomized to placebo (n=80) or to bosentan (n=77). The treatment effect (TE) of bosentan on PVR was statistically significant as compared to placebo, demonstrated as a decrease of 24.1% from baseline (95% CI, –31.5 to –16.0; *P*<.0001). Total pulmonary resistance (TE, –193 dynes×cm×s^{-5}; 95% CI, –283 to –104; *P*<.0001) and cardiac index (TE, 0.3 L×min^{-1}×m^{-2}; 95% CI, 0.14- 0.46; *P*=.0007) improved. Mean treatment effect on 6-minute walk distance was +2.2 m (95% CI, –22.5 to 26.8; *P*=.5449). Bosentan treatment was well tolerated. This study demonstrated a positive treatment effect of bosentan on hemodynamics in this patient population. However, no improvement in exercise capacity was observed.

Conclusion

CTEPH has emerged as a "dual" pulmonary vascular disease with major vessel vascular remodeling involving thrombus organization that is a target for PEA, combined with a small vessel pulmonary arteriopathy that is a principal target for classical vasodilator therapy. However, further trials are needed to define the role and appropriate end-points for assessing medical treatment in patients with CTEPH.

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