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Chronic thromboembolic pulmonary hypertension

CLINICAL REVIEW

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Chronic thromboembolic pulmonary hypertension is a rare complication of pulmonary embolism and entails high morbidity and mortality. The gold standard for treatment is pulmonary endarterectomy, which improves haemodynamics and exercise capacity, and is potentially

curative. Alternative options for the approximately one third of patients who are inoperable are percutaneous balloon pulmonary angioplasty and medical therapy. The aim of this article is to provide a clinical overview of the pharmacological, endovascular and surgical treatments for the condition.

Chronic thromboembolic pulmonary hypertension (CTEPH) belongs to Group 4 of the European classification of pulmonary hypertension (1). If untreated, the condition has a three-year mortality rate of over 30 % (2, 3). The gold standard for treatment is cardiothoracic surgery with pulmonary endarterectomy, which improves haemodynamics and exercise capacity, and is potentially curative (4). For patients who are inoperable (approximately one third), haemodynamics and exercise capacity can be improved with percutaneous balloon pulmonary angioplasty (5–7). This treatment method is a class 1 recommendation for patients who are ineligible for surgery (1). Rikshospitalet is the national centre in Norway for the investigation and treatment of chronic thromboembolic pulmonary hypertension and offers surgical, interventional and pharmacological treatment for the condition.

After an acute episode of pulmonary embolism, anticoagulant treatment usually leads to resolution of thromboembolic material within three months, with pulmonary artery pressure returning to normal (8). In a minority of patients, thrombus material does not resolve, and the patient develops chronic pulmonary embolism. No known history of venous thromboembolism is reported in 25 % of patients with chronic thromboembolic pulmonary hypertension (9). The annual incidence of the condition in Europe is estimated to be 3–5 patients per 100,000 population (10). Available Norwegian data suggest a lower annual incidence in Norway of < 1 per 100,000 population (11, 12). Box 1 gives an overview of predisposing factors for the disease (13).

Box 1 Predisposing factors for chronic thromboembolic pulmonary hypertension (13).

Ventriculoatrial shunt

Infected pacemaker electrodes

Splenectomy

Recurrent venous thromboembolism

Thyroid replacement hormones

Antiphospholipid syndrome

Malignancies

Inflammatory bowel disease

Non-O blood groups

Key differential diagnoses considered early in the workup are lung disease, heart disease and pulmonary hypertension of other causes. Other conditions that cause pulmonary artery obstruction include sarcoma, other malignant and non-malignant tumours, congenital pulmonary artery stenosis, foreign bodies and large vessel

vasculitis (14). This article provides an overview of the pharmacological, endovascular and surgical treatments for chronic thromboembolic pulmonary hypertension, based on a discretionary selection of the literature and the authors' own clinical experience.

Pathophysiology and symptoms

The cause of chronic thromboembolic pulmonary hypertension is incomplete resolution of thromboembolic material, which can be exacerbated or caused by thrombus angiogenesis, decreased fibrinolysis and endothelial dysfunction (15). Thromboembolic material leads to occlusion or narrowing of large pulmonary arteries, but small-vessel disease also occurs, with lesions resembling those seen in pulmonary arterial hypertension (13). The lesions result in increased pulmonary vascular resistance, which if left untreated can lead to progressive right heart failure and death.

The main symptoms of chronic thromboembolic pulmonary hypertension are dyspnoea and exercise intolerance. Later stage symptoms include chest pain, syncope on exertion and clinical signs of right heart failure.

Diagnostic workup

The first step in the workup when CTEPH is suspected is usually echocardiography. Doppler measurement of tricuspid regurgitation velocity can be used to estimate pulmonary artery pressure. In pulmonary hypertension, echocardiography demonstrates left displacement of the interventricular septum, reduced left ventricular filling and reduced stroke volume (Figure 1). Persistent dyspnoea three months or more after pulmonary embolism should be investigated with echocardiography, followed by further workup if there are signs of pulmonary hypertension.

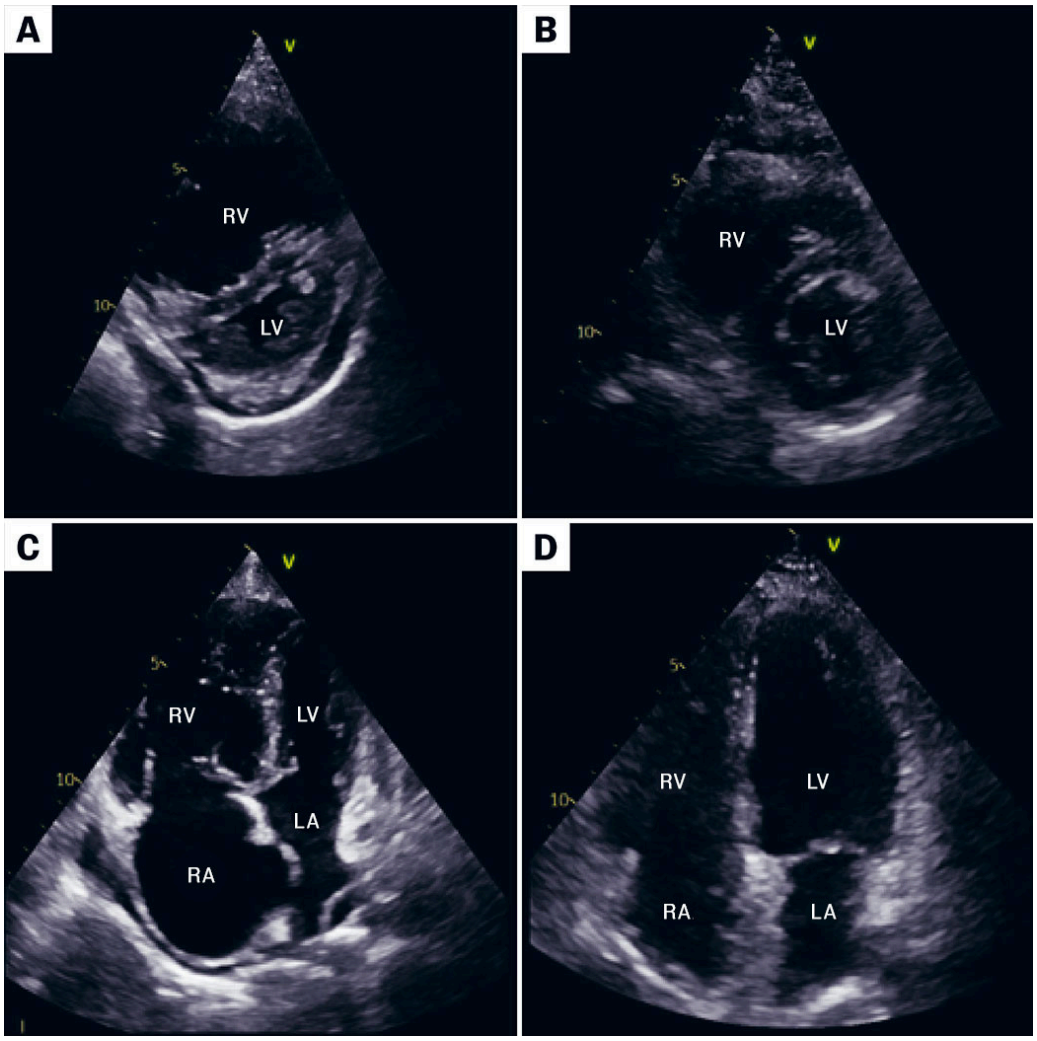

Figure 1 Panels A and B show echocardiography from the parasternal short axis view before and after pulmonary endarterectomy. The pre-surgery image (A) demonstrates pressure overload of the right ventricle (RV), with curving of the interventricular septum towards the left ventricle (LV). The post-surgery image (B) demonstrates normalisation of the septal shape. Panels C and D show echocardiography from the same patient in an apical 4 chamber view before and after surgery. The pre-surgery image (C) demonstrates a severely dilated right ventricle, which is normalised after surgery (D). LA = left atrium, RA = right atrium.

Ventilation/perfusion scintigraphy has higher sensitivity than CT angiography for detecting chronic pulmonary embolism, but CT angiography is key following initial echocardiography (16). Invasive pulmonary angiography shows stenoses, occlusions and perfusion defects, and together with CT angiography it is crucial for the planning of pulmonary endarterectomy and percutaneous balloon pulmonary angioplasty.

The diagnosis of pulmonary hypertension is made by right heart catheterisation. Chronic pulmonary embolism leads to precapillary pulmonary hypertension, defined as mean pulmonary artery pressure > 20 mmHg and pulmonary vascular resistance > 2 Wood units, in the absence of elevated left-sided filling pressure (pulmonary arterial wedge pressure ≤ 15 mmHg) (1).

The diagnosis of chronic thromboembolic pulmonary hypertension requires thromboembolic lesions and pulmonary hypertension after a minimum of three months of anticoagulant treatment. All patients with pulmonary hypertension with no other obvious cause should undergo investigation for the condition.

Treatment

The treatment of chronic thromboembolic pulmonary hypertension is multidisciplinary and often consists of a combination of medical therapy and surgical and interventional treatment. Treatment selection is determined by the anatomical extent of the thromboembolic lesions (proximal, distal or microvascular) and the degree of comorbidities.

Pulmonary endarterectomy is appropriate for proximal to distal lesions in the pulmonary artery. If lesions are predominantly distal, percutaneous balloon pulmonary angioplasty is most suitable, while surgical and interventional treatment may be indicated in patients with both proximal and distal lesions in the pulmonary artery. Microvascular lesions are treated with medical therapy only. The aim of treatment is to reduce resistance in the pulmonary vasculature, normalise pulmonary artery pressure, lower the symptom burden, increase quality of life and improve survival.

Medical therapy

Medications for pulmonary artery hypertension can also be used for chronic thromboembolic pulmonary hypertension. Riociguat (a soluble guanylate cyclase stimulator) increases 6-minute walking distance and reduces pulmonary vascular resistance in inoperable patients (7, 17), and is recommended in this indication (1). This is also the case for persistent pulmonary hypertension following pulmonary endarterectomy.

Patients with chronic thromboembolic pulmonary hypertension require lifelong anticoagulant therapy, and vitamin K antagonists have traditionally been the treatment of choice. These medications have not been compared with direct oral anticoagulants in randomised clinical trials in this indication. Observational studies have demonstrated a similar bleeding rate, but a higher thromboembolism recurrence rate with direct oral anticoagulants (18, 19).

Pulmonary endarterectomy

Pulmonary endarterectomy is performed via sternotomy using cardiopulmonary bypass. Bilateral endarterectomy down to a segmental and subsegmental level is performed under deep hypothermia (20 °C) and periods of total circulatory arrest (Figure 2). Surgery must be performed by experienced surgeons with a team that is able to manage postoperative circulatory and pulmonary complications. Experience with extracorporeal membrane oxygenation (ECMO) is necessary.

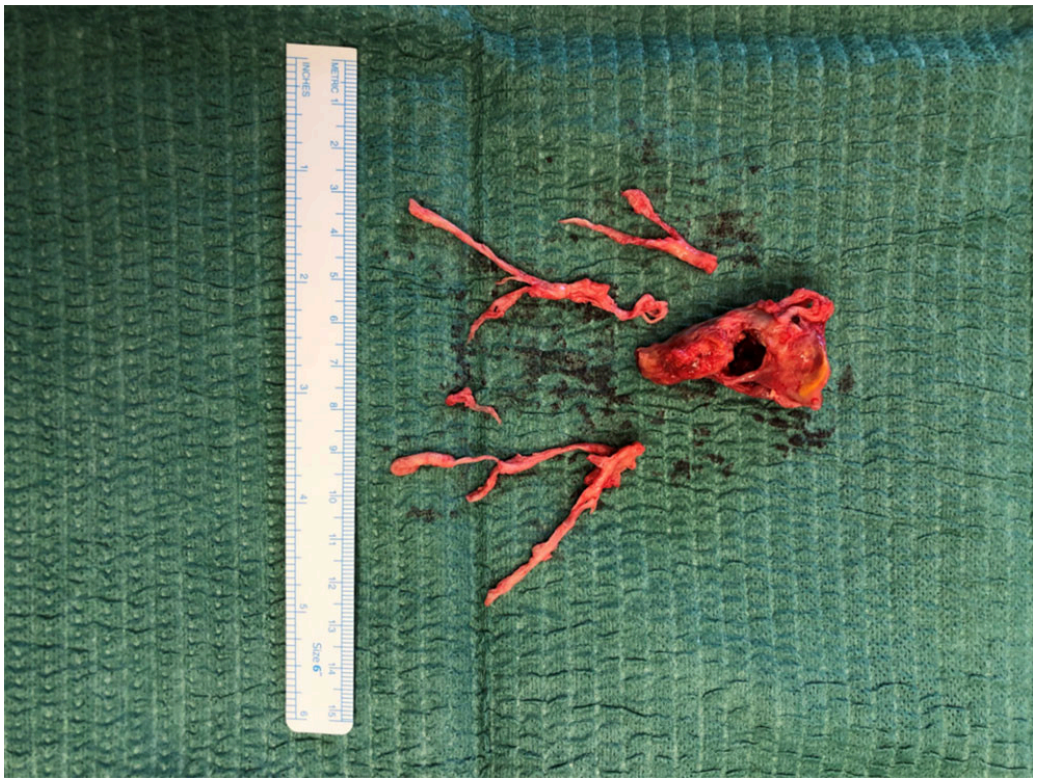

Figure 2 Intraoperative image of thromboembolic material from the right lung following pulmonary endarterectomy.

Severe underlying parenchymal lung disease is a relative contraindication to pulmonary endarterectomy (20). Factors that may make cardiothoracic surgery inadvisable are advanced age and extensive comorbidities. Three groups are not offered pulmonary endarterectomy: operable patients who do not want to undergo surgery, operable patients with severe comorbidities where the benefits of surgery are outweighed by the risks, and patients with technically inoperable lesions (usually because the location of the lesions is too distal).

Balloon pulmonary angioplasty

Percutaneous balloon pulmonary angioplasty has been performed at Rikshospitalet since 2003 (Figure 3) (5). The method is primarily used in patients with peripheral stenoses and occlusions in pulmonary vasculature that are deemed unsuitable for surgery, patients with persistent pulmonary hypertension following pulmonary endarterectomy and patients who are opposed to surgery (1). Percutaneous balloon pulmonary angioplasty is also considered in patients with technically operable lesions for whom surgery has an unfavourable benefit-risk ratio. Since the technique is primarily performed at a subsegmental level and more peripherally, it requires the opening and/or balloon dilation of a large number of arterial branches, and a micro-guidewire must be advanced each time. This can entail complications including vascular perforation and haemoptysis, which are managed with balloon inflation or coil embolisation of the injured vessel to stop the bleeding. In our data material, we have reported haemoptysis in 7 % and wire perforation in 5.4 % of procedures (21).

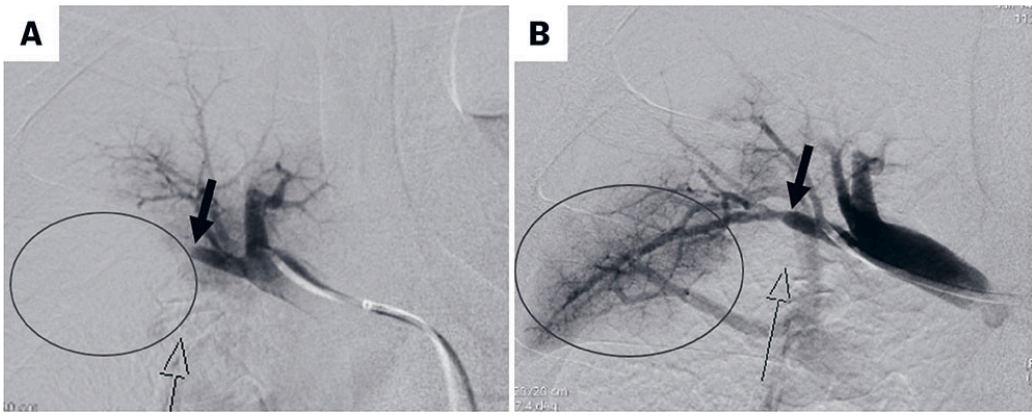

Figure 3 Angiography before (A) and after (B) balloon pulmonary angioplasty of an occluded segmental artery to the right upper lobe (arrows). Change from complete perfusion defect (ring) to good contrast uptake (ring) in the parenchyma and clear venous drainage (transparent arrow).

As with pulmonary endarterectomy, balloon pulmonary angioplasty entails a risk of reperfusion oedema and temporary worsening of dyspnoea and hypoxia, with a fatal outcome in the most severe cases (22). Treatment is time-consuming and involves the use of considerable quantities of contrast agent. Therefore, percutaneous balloon pulmonary angioplasty is performed in multiple sessions with a smaller number of pulmonary segments being treated each time. This reduces the risk of reperfusion oedema.

In patients without improvement from surgical, interventional or pharmacological treatment, lung transplantation is a last treatment option for severe chronic thromboembolic pulmonary hypertension. Lung transplantation has not been performed for this indication in Norway for ten years.

Prognosis and efficacy of treatment

Pulmonary endarterectomy produces good results, with a three-year survival rate of 94 % in a large international registry (22). In the 1970s and 1980s, perioperative mortality was over 15 %, but it is now below 5 % (22). The results of pulmonary endarterectomy and percutaneous balloon pulmonary angioplasty are dependent on the surgeon's level of experience. Patients treated with percutaneous balloon pulmonary angioplasty have a three-year survival rate of 92–95 % (23). Balloon pulmonary angioplasty is not as effective as pulmonary endarterectomy in reducing pulmonary vascular resistance, but centres in Japan report a reduction in pulmonary pressure exceeding that achieved in Europe and North America, and approaching levels expected after pulmonary endarterectomy. The reasons for this may be differing practices in patient selection, phenotype variations and differing approaches to the management of complex vascular lesions with percutaneous balloon pulmonary angioplasty (24).

Whether the differing results for balloon pulmonary angioplasty and pulmonary endarterectomy solely represent differences between the two methods or whether patient-related factors are significant has been the subject of discussion. Currently, pulmonary endarterectomy is the treatment of choice for operable patients, while balloon pulmonary angioplasty is offered to patients deemed inoperable (1). However, both procedures are appropriate in some patients. It has not been established which

treatment is best in that situation. A randomised multicentre study (NCT05110066) is underway in which patients who are eligible for both pulmonary endarterectomy and balloon pulmonary angioplasty are randomised to these treatments in a ratio of 1:1. Norwegian data indicate an annual incidence of chronic thromboembolic pulmonary hypertension of just below 1 per 100,000 population.

This is considerably lower than the reported incidence of chronic thromboembolic pulmonary hypertension in other countries (10), and in view of the fact that only 10–20 patients are referred to Rikshospitalet each year (unpublished referral data from Rikshospitalet), there is reason to suspect considerable underdiagnosis of the condition.

Summary

Chronic thromboembolic pulmonary hypertension is associated with a high disease burden and mortality. Since a potentially curative surgical treatment option is available, it is vital that the condition be diagnosed. Balloon pulmonary angioplasty and modern medical therapy are alternative options for inoperable patients.

The article has been peer-reviewed.

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