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Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare but life-threatening complication of acute pulmonary embolism (PE). This entity is the consequence of a persistent obstruction of the pulmonary arteries and progressive vascular remodeling. Some patients with CTEPH do not have a history of classic pulmonary embolism symptoms. The diagnostic process to detect CTEPH should include ventilation-perfusion scintigraphy, which has a high sensitive and negative predictive value (nearly 100%) and CT angiography demonstrating typical features of CTEPH (occlusion of pulmonary arteries, mosaic perfusion or intraluminal bands or webs). Patients suspected of having CTEPH must be referred to an experienced center in order to complete the diagnostic workup (right-heart catheterization and pulmonary angiography) and determine the best treatment. Pulmonary endarterectomy (PEA) remains the treatment of choice for CTEPH and is associated with excellent long-term results and a highly curative rate. Patients with inoperable CTEPH are given medical and interventional modalities.

Keywords: thromboembolism, pulmonary hypertension, pulmonary endarterectomy

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by a persistent obstruction of the pulmonary arteries after a pulmonary embolism (PE) that has not resolved despite 3 months of medical therapy with anticoagulants and is defined as a raised mean pulmonary artery pressure (at least 25 mmHg at rest), a pulmonary capillary wedge pressure of ≤ 15 mmHg and at least one (segmental) perfusion defect detected by lung scanning, multi-detector computed tomographic angiography or pulmonary angiography [1, 2]. CTEPH is a form of pulmonary artery hypertension (PAH) characterized by the occlusion of the pulmonary...
arteries by organized fibrotic thrombi leading to increased pulmonary vascular resistance (PVR). The consequential effect is dyspnea, right heart failure and even death. CTEPH is classified as group IV according to the WHO classification of pulmonary hypertension [3]. Some patients may present symptoms and signs of CTEPH but no pulmonary hypertension; this presentation should be termed chronic thromboembolic disease, although the management of these patients does not differ to that of the classic CTEPH patients.

The most common cause of CTEPH is non-resolving acute pulmonary embolism (PE) and can occur after one or multiple episodes. Occasionally, CTEPH may develop after in situ pulmonary artery thrombosis which could be associated with the inflammation of vessel walls [4].

CTEPH can be mistaken for PE; it is important to differentiate between these, in order to diagnose the chronic disease as early as possible. Once the diagnosis of CTEPH is made, careful patient selection in experienced centers is preferable in order to obtain the best results for these patients.

Because of its unique characteristics, CTEPH is the only form of PH that can be curable by pulmonary endarterectomy (PEA); although, this is a complicated surgery and not every patient may be fit to undergo such a procedure. The most benefited patients are those who present a proximal compromise [5].

CTEPH remains underdiagnosed and carries a poor prognosis. Medical and interventional treatment are options for patients that are not surgical candidates. In this chapter, the available information on the surgical treatment of CTEPH is summarized.

2. Historical note

The first description of the CTEPH was made in 1928 by Dr Ljungdahl on two symptomatic patients with chronic obstruction of the pulmonary arteries who ultimately died of right heart failure [6]. The first successful embolectomies for recurrent pulmonary embolism were reported by Allison and colleagues in 1958 and by Snyder and colleagues in 1962 [7, 8]. Then, Cabrol et al. refined the technique using a lateral thoracotomy in order to obtain access to distal pulmonary branches [9]. In 1980, Daily et al. reported the use of cardiopulmonary bypass (CPB) and hypothermic circulatory arrest, allowing the reduction of severe back bleeding and improving the visualization of the pulmonary arteries during endarterectomy [10]. This is the current preferred technique.

3. Morphology

The process of the disease typically occurs in the proximal pulmonary arteries from trunk to sublobar levels. The distal vasculature remains patent. This presentation is the basis for the surgical approach of CTEPH. The disease may develop from a single embolic episode with non-resolution of large thrombi or from repeated thromboembolic episodes [11].
remaining unobstructed pulmonary arteries are exposed to high flow and eventually high pressure. Then, proximal patent pulmonary arteries enlarge, and the distal arterial vasculature develops changes of pulmonary hypertension such as intimal proliferation and medial hypertrophy. The characteristic diagnostic finding of primary pulmonary hypertension, the plexiform lesion, is also observed in CTEPH [12]. The occlusive process is usually central, incipient and unresponsive to antithrombotic or anticoagulant therapy when the thrombi become fibrotic and endothelialized. The thrombotic material has well-organized fibrous tissues, penetrating blood vessels, elastic fibers and no endothelial cells. The arterial layers demonstrate intimal and medial hyperplasia. Infarction of the lung tissue is rarely observed [2]. These microvascular changes explain why CTEPH is a progressive disease even in the absence of recurrent thromboembolic events.

4. Epidemiology

The estimated prevalence of CTEPH after acute pulmonary embolism is 0.1–4% after 2 years [2, 13–16]. The median age at diagnosis is 63 years, and both genders are equally affected [17]. The risk of developing CTEPH is increased in patients with recurrent venous thromboembolism, echocardiographic signs of pulmonary hypertension at the initial presentation and large perfusion defects. Common risk factors for venous thromboembolism (factor V Leyden, factor II mutation) are not associated with the development of CTEPH except for the presence of antiphospholipid antibodies, which predispose patients to acute venous thromboembolism and CTEPH [1, 18–20]. Different disorders considered to be risk factors include inflammatory bowel disease, splenectomy, myeloproliferative disorders, chronic osteomyelitis and the presence of permanent central venous lines, pacemakers or ventriculoatrial shunts [20–23]. These disorders are associated with chronic inflammation, an increased risk of repeated bloodstream infection or both, which may contribute to the non-resolution of thromboembolic material [1]. C-reactive protein is also implicated in the development of CTEPH [24]. Infection of thrombotic material by blood-borne pathogens could predispose to the development of CTEPH, specially in patients with permanent central venous lines, pacemakers or ventriculoatrial shunts [25].

5. Natural history

It is relatively infrequent to find a complete resolution of pulmonary embolism. If adequate anticoagulation therapy has been done, more than 50% of patients have residual perfusion defects 6 months after the diagnosis of pulmonary embolism [26]. However, the majority of these patients do not develop florid chronic pulmonary hypertension; in fact, patients presenting signs of pulmonary hypertension during an episode of acute pulmonary embolism are unlikely to develop CTEPH, and most of these patients recover a stable phase of right ventricular functions within 40 days [13]. Some patients, however, present persistent pulmonary hypertension and others develop pulmonary hypertension after a symptom-free interval that
can last from months to years \[14\]. Hemodynamic deterioration may be the result of recurrent thromboembolism or in situ pulmonary artery thrombosis. Without intervention, survival is compromised and proportional to the degree of pulmonary hypertension at the time of diagnosis \[27, 28\]. To remind, pulmonary hypertension is not a feature of acute pulmonary embolism since the right ventricle (RV) is incapable of generating high pressures in early stages. In that order, any patient presenting with acute pulmonary embolism and elevated pulmonary resistances may already have CTEPH. In a study, the 5-year survival rate was 30% among patients with a mean pulmonary pressure > 40 mmHg at time of diagnosis, and it dropped dramatically to 10% among those with a mean pulmonary pressure > 50 mmHg \[29\]. In another study, a mean pulmonary artery pressure of 30 mmHg marked the threshold for poor prognosis \[30\].

6. Clinical features and diagnosis

6.1. Symptoms

In general, symptoms do not develop until months or years after the embolic event \[2\]. They occur as a result of right ventricular failure or pulmonary hypertension. Progressive dyspnea on exertion is the predominant symptom of CTEPH \[11\]. Additionally, patients might present with fatigue, substernal chest pain with exercise, pleuritic pain and hemoptysis \[11, 31\].

6.2. Signs

Relevant physical findings are related to right heart failure: jugular venous distention, ascites, hepatomegaly and peripheral edema. The right ventricle may be enlarged and palpable near the lower left sternal border. The pulmonic second sound is accentuated and split. A murmur of tricuspid regurgitation might be heard in severe right heart failure.

CTEPH should be considered in all patients who have an evident history of acute pulmonary embolism. Despite 25% of the patients diagnosed as having CTEPH, there are no documented acute pulmonary embolism events \[32\]. Thus, CTEPH should be suspected in any patient with otherwise unexplained pulmonary hypertension.

6.3. Diagnostic studies

The chest radiograph may demonstrate right ventricle enlargement and the prominence of central pulmonary arteries. The ECG frequently shows RV hypertrophy with strain, right axis deviation, ST depression, T-wave inversion in the anterior precordial leads and occasionally right bundle branch block \[31\]. Transthoracic echocardiography provides the initial objective evidence for the presence of PAH. Findings in chronic thromboembolic and other forms of PAH include the enlargement of right cardiac chambers, tricuspid regurgitation as a consequence from this enlargement, the flattening or paradoxical motion of the interventricular septum and impaired left ventricular diastolic filling not caused by primary left ventricular
diastolic dysfunction or valvular heart disease [33, 34]. Pulmonary function studies are necessary to exclude restrictive or obstructive pulmonary parenchymal disease as the cause of PAH. Ventilation-perfusion scanning is the preferred diagnostic tool because of its high sensitivity and a negative predictive value of almost 100% [35]. In that order, CTEPH is practically ruled out if the scan is normal [35]. A lung perfusion scan showing at least one segmental or larger defect is suggestive of chronic vascular obstruction [2]. Often, the scan underestimates the severity of an obstructive disease [36, 37]. Perfusion defects can also occur in other disorders such as pulmonary veno-occlusive disease, pulmonary vasculitis, fibrosing mediastinitis or malignant disease [38–40]. CT scanning and MRI of the chest are important diagnostic tools and are being used with increasing frequency [41, 42]. If imaging suggests the presence of CTEPH, patients should be evaluated with right-heart catheterization to measure the right ventricle and pulmonary artery pressures and to evaluate the presence of shunting at the atrial or ventricular level. Pulmonary angiography is safe in patients with chronic pulmonary hypertension [2, 43]. Typical findings include dilated proximal pulmonary arteries, varying degrees of obstruction of lobar arteries, filling defects, web or bands or thrombosed vessels suggesting the presence of organized thrombi [44]. In order to avoid repeat procedures, angiography should be done in a center that assesses the patient’s suitability for surgery. A general screening after acute pulmonary embolism is not recommended, given the low risk of developing CTEPH after such an event [45–47]. Care must be taken, however, in patients who show symptoms after an episode of acute pulmonary embolism. Echocardiography is widely used when suspecting pulmonary hypertension. A diagnostic approach that combines an electrocardiogram with no signs of hypertrophy in the right ventricle and a normal natriuretic peptide (N-terminal-pro-brain-type fragment) has a negative predictive value of 99% for CTEPH [48]. Angioscopy is an alternative tool adjunct to angiography, CT or MRI when these modalities cannot establish the diagnosis properly [49].

7. Treatment

Patients diagnosed with CTEPH should have life-long anticoagulation, even those who underwent successful PEA. The target international normalized ratio is 2.0 to 3.0. The use of filters in the inferior vena cava remains controversial [50]. Currently, the use of these filters is indicated when therapeutic anticoagulation is not feasible or when recurrent venous thromboembolism occurred despite sufficient anticoagulation [51]. Prospective studies on this matter are warranted.

7.1. Surgical selection

The most important criterion that determines whether a patient with CTEPH might be a candidate for PEA is the presence of surgically accessible lesions. PEA should be considered in symptomatic patients who have hemodynamic or ventilatory impairment at rest or with
The decision to proceed with PEA in patients with CTEPH is difficult based on their preoperative pulmonary hemodynamic profile and the anticipated improvement in these hemodynamics postoperatively [27]. The basis for this concern is that the elevated vascular resistance not only arises from central (surgically accessible) vessels but also from secondary, small vessels with arteriopathy [27]. A preoperative approach should differentiate these two components and anticipate the postoperative hemodynamic outcome. This important issue remains relatively subjective. There is a high correlation between the postoperative level of pulmonary vascular resistance (PVR) and mortality. In a study by Jamieson and colleagues including 500 consecutive operated patients with an overall mortality of 4.4%, 77% of deaths were related to residual high pulmonary artery pressures. Patients with a postoperative PVR > 500 dynes-sec-cm\(^{-5}\) had a mortality rate of 30.6% compared to 0.9% in patients with a postoperative PVR < 500 dynes-sec-cm\(^{-5}\) [53]. The majority of patients who undergo a PEA have a PVR > 300 dynes-sec-cm\(^{-5}\). Experienced centers report a range of preoperative PVR between 700 and 1100 dynes-sec-cm\(^{-5}\) [53–58]. Symptoms patients at the lower end of these values include those with involvement limited to one pulmonary artery, those accustomed to a vigorous activity and those who live at high altitudes [52]. Operations should also be considered for patients with nearly normal pulmonary hemodynamics at rest but marked pulmonary hypertension induced by exercise. The only absolute contraindication to operation is the presence of severe underlying obstructive or restrictive lung diseases [52]. The most important risk factor for surgery is the presence of high pulmonary resistances without visible abnormalities by angiography [53]. Older patients and severe RV failure are associated with increased risk but do not preclude surgery.

### 7.2. The technique of operation

This is the description of the current accepted and most widely used technique for PEA. Electroencephalographic recording is essential to ensure the absence of cerebral activity before circulatory arrest is induced. The patient's head is involved in a cooling jacket. Standard preparations for the establishment of cardiopulmonary bypass (CPB) are made. A median sternotomy is performed. Cannulas are inserted into the ascending aorta and both vena cavae, which are encircled with tapes. Immediately after CPB starts, cooling is initiated (including the head jacket and the cooling blanket). This could take 45 minutes to 1 hour [59]. A venting catheter is placed in the left atrium through the upper right pulmonary vein. If the patient's condition allows it, autologous whole blood is withdrawn for later use. The deficit can be replaced with a crystalloid solution. The aorta is clamped and cold blood cardioplegia is given. Additional myocardial protection could be done by subsequent infusions of cold cardioplegic solution, every 15 to 20 minutes. During the cooling period, mobilization of the right pulmonary artery from the ascending aorta is made as well as the mobilization of the superior vena cava. Also, methylprednisolone (7 mg/kg) and thiopental (10–15 mg/kg) are administered to favor the neuroprotective effect of hypothermia. Mannitol (0.3–0.4 mg/kg) and furosemide (100 mg) are infused to preserve the renal function. Once the core temperature has reached 12–14°C and the electroencephalogram becomes isoelectric, circulatory arrest is established [60]. Both encircling tapes of superior and inferior vena cava are secured to ensure complete drainage and to avoid air embolization into the venous cannulae during
circulatory arrest. An incision is made in the right pulmonary artery between the aorta and the superior vena cava (Figure 1), extending the incision toward the right lower lobe artery, a few millimeters farther from the takeoff of the middle lobe artery (Figure 2). Using a sharp dissector can help establish an endarterectomy plane (Figure 3). The intima and a portion of the media are removed. Establishment of the correct plane is essential—too deep will result in artery perforation, too shallow will result in an inadequate endarterectomy [61]. When the adequate plane is achieved, the layer will dismount easily. The core of the thrombus is dissected in a circumferential manner (Figure 4) and removed from each subsegmental branch and from the pulmonary artery (Figure 5). Gentle traction with forceps is applied to the core as well as opposite force to the pulmonary wall that will facilitate the removal of the specimen (Figure 6). The remaining core is removed from the proximal portion of the right pulmonary artery (Figure 7). The arteriotomy is closed with a continuous 5–0 or 6–0 polypropylene suture (Figure 8). If needed, a pericardial patch can be used that is sutured into place with a continuous 6–0 polypropylene suture. The period of circulatory arrest ranges from 20 to 25 minutes. Cold blood is reperfused for 8–10 minutes between these intervals. As for the left side, the incision begins in the pulmonary trunk and extends onto the left pulmonary artery to the level of the pericardial reflection (Figure 9). Endarterectomy of the left side mirrors that of the right pulmonary artery. The core is removed from the upper lobe artery and each subsegmental branch. The artery is closed in a continuous fashion or with
Figure 2. Exposure of distal right pulmonary artery between aorta and superior vena cava. Dashed line indicates line of incision.

Figure 3. Endarterectomy plane is facilitated with a sharp dissector.
Figure 4. Circumferential isolation of the core of the thrombus and extraction from upper lobe and distal pulmonary artery.

Figure 5. Extraction of the core of the thrombus.
Figure 6. Separation of core from proximal pulmonary artery.

Figure 7. Complete extraction of core specimen.
Figure 8. Arteriotomy is closed with a continuous 5–0 or 6–0 polypropylene suture.

Figure 9. Incision in left pulmonary artery (dashed line) begins in the pulmonary trunk and extends onto the left pulmonary artery.
an autologous pericardial patch. CPB begins and rewarming of the patient is established. If any other defects are present, such as patent foramen ovale or atrial septal defect, these are corrected to prevent the right-to-left shunting. If additional procedures are required, they are made during rewarming [62]. Right ventricle remodeling occurs within a few days, so, any tricuspid regurgitation rarely needs repair or replacement [61, 62]. Deairation maneuvers from cardiac chambers are performed, CPB is discontinued and the procedure is completed in the usual fashion.

7.3. Postoperative care

An FiO\textsubscript{2}, high enough to maintain SaO\textsubscript{2} > 95%, during mechanical ventilation, is preferred. PaCO\textsubscript{2} should be ≤ 35 mmHg. An important postoperative problem is reperfusion of the pulmonary edema and occurs in approximately 10% of patients [61]. Lung injury can develop within the first 2 days of exhibiting hypoxemia and radiographic infiltrates in areas where endarterectomy has been done [63]. Treatment for this condition includes maintaining a SaO\textsubscript{2} >90% and positive end-expiratory pressures of 5–10 cm. Prostaglandin E1 at 0.01–1 mg/min and inhaled nitric oxide (20–40 parts per million) may be useful. Diuretics use is often required to reduce the incidence of pulmonary edema [64]. Since the reperfusion injury is neutrophil mediated, treatment with agents that block the selectin-mediated adhesion of leukocytes to the endothelium (Cylexyn) could be useful [63]. Extracorporeal support has been used in selected patients with serious reperfusion injury [52]. Permanent anticoagulation with warfarin is started on the second postoperative day [60].

7.4. Results

Experienced centers have a mortality that ranges from 4.4 to 21% [53, 64–68]. Risk factors commonly associated with mortality in the early postoperative period are RV failure related to residual pulmonary hypertension, reperfusion lung injury and CPB duration [10, 52, 53]. Survival rates are almost the same when comparing patients who underwent pulmonary endarterectomy alone with other patients with additional procedures (5.8 vs. 6.7%, respectively) [62]. In the largest study with patients undergoing pulmonary endarterectomy, the 6-year survival rate was 75% (Figure 10) [69]. The most common causes of late death were recurrent pulmonary embolism and persistent pulmonary hypertension [69]. Hemodynamic outcomes after pulmonary endarterectomy for most patients are favorable [56, 64–67, 70–74]. The only long-term study on hemodynamics after PEA observed persistent pulmonary hypertension in 24% of patients who had pulmonary vascular resistance of more than 500 dynes-sec-cm\textsuperscript{-5} after 4 years [75]. Dramatic reduction and, sometimes, normalization of the pulmonary artery pressure and pulmonary vascular resistance can be achieved. The mean reduction in pulmonary vascular resistance is approximately 65% [52]. Most patients are in New York Heart Association Functional Classification, class III or IV, before surgery; after the procedure, they can improve to class II or I and are able to resume normal activities [11, 69, 70]. Recurrent thromboembolism requiring a second endarterectomy has occurred in several patients in whom anticoagulation was discontinued or given improperly [76].
8. Conclusions

CTEPH is a life-threatening complication of pulmonary embolism. There are notable differences in the treatment from that of other forms of pulmonary hypertension. A complete diagnostic assessment should be done in those patients with unexplained pulmonary hypertension. These studies should include a ventilation-perfusion scintigraphy, right-heart catheterization and pulmonary angiography. It is recommended though that the final diagnostic and therapeutic approach should be performed in experienced centers.

PEA is the preferred treatment and remains the only potentially curative approach. For patients in whom surgery is not an option, riociguat is the only approved drug that improves hemodynamics and exercise capacity. Balloon pulmonary angioplasty is yet to be proven effective in the treatment of these patients. An increased understanding of the prevalence of this condition and opportunities of surgical cure should benefit a larger volume of patients.

Author details

Fabian Andres Giraldo Vallejo
Address all correspondence to: fabiangiraldomd@gmail.com
Heart Institute of Bucaramanga, Bucaramanga, Colombia
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